A Synthetic Approach to the Sarain Core and Development of New Thioamide-Based Methodologies

A thesis presented to University College London in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Adam Ellwood

Supervisor: Dr M J Porter

University College London

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Declaration

I, Adam Ellwood, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this information has been indicated in the thesis.

Abstract

Sarain A is a marine alkaloid that was isolated from the Mediterranean sponge *Reniera sarai*; the alkaloid possesses antibacterial, insecticidal and antitumour properties. As a result of the intriguing structure of this alkaloid, it has quickly become a popular target for organic chemists. Arguably the most challenging part of its synthesis is the tricyclic core, which is surrounded by two macrocyclic rings. This thesis describes two separate approaches towards the core, both utilising a thia-Claisen rearrangement as a key step.

The first approach involved the ring expansion of a 5,5-bicyclic aminal to form an iminium ion intermediate which could be transformed into the core. However, the inherent lack of nucleophilicity of an *N*-tosyl sulfonamide nitrogen atom in the bicyclic aminal made it difficult to perform the ring expansion. The second method involved a modification of an acid catalysed rearrangement previously attempted within the Porter group; in the previous approach, a differentially protected bicyclic aminal opened with cleavage of a C-NTs rather than a C-NBn bond, leading to an undesired tricyclic product. In the newly devised route, the protecting groups on the two nitrogen atoms of the bicycle were reversed in order to encourage ring opening in the desired fashion; however, the only attempt at this step did not result in the formation of the sarain core.

In a different project that is related to the aforementioned research, a diastereoselective thia-Claisen rearrangement was developed which allows the formation of a key intermediate en route to the sarain core, in enantiomerically pure form. To achieve this, thia-Claisen rearrangements were carried out on several *S*-allyl *N*,*S*-ketene acetals bearing a stereogenic centre on the allyl portion of the molecule to give diastereomeric ratios of 2:1 to 30:1. Interestingly, introduction of a bromine atom onto the double bond of the allylic portion of the precursor increased and *reversed* the diastereoselectivity.

Finally, following a discovery that was made whilst working towards the sarain core, a novel reaction for the high-yielding conversion of a wide range of alcohols into iodides using a thioiminium salt has been investigated and optimised. The reaction conditions are essentially neutral, no aqueous workup is required, many functional groups can be tolerated and reaction times are generally short. Furthermore, the thioiminium salt can be stored for long periods without degradation. This type of chemistry has since been further examined, and it can now be used to allow the conversion of alcohols directly into sulfide products that are precursors in Julia-Kocienski reactions.

Contents

Acknowledgements

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Thanks to Anne for teaching me almost all my lab skills when I first started out, and for providing great support throughout my PhD. Next there's Pui Shan and Amandeep; thanks also for the help during the early years in the lab – Pui Shan, I miss our Hollyoaks conversations! (I'm sure you said this in your thesis too? haha), and Amandeep, you'll be glad to know that I still try to incorporate your name into songs that I hear on the radio! Also, thank you Abil for your help with NMRs over the years!

Then there's Moussa and Jai – Mous, you are just too funny! I will never forget the laughs we had in the lab. There is nothing quite like winding you up! One standout moment for me, if I had to pick only one, was you taking your shirt off in the lab because you were hot (naughty boy!), and then Anne walked past and said (in a very calm voice): "Moussa.....put your shirt on''. Jai, you are the nicest guy I know. You will do anything for a friend and I wish you all the best during the rest of your PhD. We had a good time during my last 2 years – I miss our music chats! You two will be good friends of mine forever, and I'll be seeing you both soon.

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I'll miss UCL chemistry. It's been a long but worthwhile journey. Over and out!

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
$[\alpha]_D$	Specific rotation
$A^{1,3}$-strain	Allylic 1,3-strain
aq.	Aqueous
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
CAM	Cerium ammonium molybdate
CAN	Cerium(IV) ammonium nitrate
Cbz	Carbobenzyloxy
COSY	Correlation spectroscopy
*m*CPBA	*meta*-Chloroperbenzoic acid
d	Day(s)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
o-DCB	*ortho*-Dichlorobenzene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess

equiv.	Equivalent(s)
FTIR	Fourier transform infrared
GC	Gas chromatography
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
h	Hour(s)
imid.	Imidazole
IR	Infrared
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
Lit.	Literature
LUMO	Lowest unoccupied molecular orbital
min.	Minutes
MOM	Methoxymethyl
mpt.	Melting point
Ms	Methanesulfonyl
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nr	No reaction
Ns	4-Nitrobenzenesulfonyl
pK_a	Acid dissociation constant

PMB	*para*-Methoxybenzyl
RCM	Ring closing metathesis
rt	Room temperature
sat.	Saturated
S_N1	Nucleophilic substitution unimolecular
S_N2	Nucleophilic substitution bimolecular
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	4-Toluenesulfonyl
UCL	University College London

1 Introduction

1.1 The structure of the sarain alkaloids

The marine environment contains a variety of organisms with secondary metabolites that are noticeably different to those found in land-based life. Not only are a large number of these molecules structurally intriguing, but many possess potent biological activity, and therefore are of great interest to the pharmaceutical industry.

Over the last few decades, many alkaloids have been isolated from marine species. One fascinating group of such alkaloids, known as the sarains, was extracted from a Bay of Naples sponge, *Reniera sarai*, by Cimino and co-workers in the mid 1980s.[1] The main metabolites are divided into two groups, each containing alkaloids with a distinct polycyclic skeleton. The first group consists of sarains 1-3 (**1**-**3**, Figure 1) and isosarains 1-3 (**4**-**6**, Figure 1); the latter differ only from sarains 1-3 in their stereogenic centres at C1, C2 and C9, all of which are inverted.[1,2,3,4] The common feature of these alkaloids is a *trans*-fused quinolizidone system, bound to an unsaturated piperidine ring, both directly and via two hydrocarbon chains.

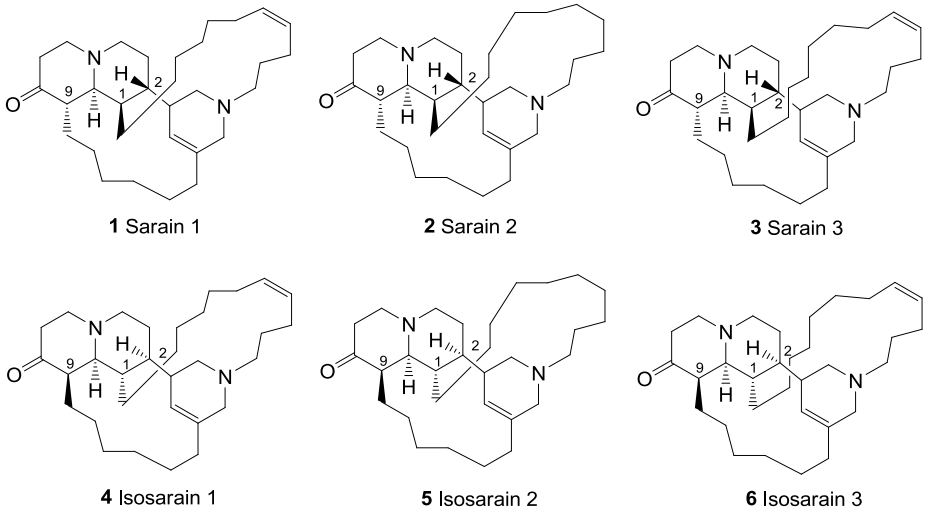


Figure 1 Sarains 1-3 (**1**-**3**) and isosarains 1-3 (**4**-**6**)

The second group of metabolites comprises sarains A-C (**7**-**9**, Figure 2).[5,6] The intriguing and unusual structure of these alkaloids consists of a fused central core containing a diazatricycloundecane cage, attached to a 14-membered ring. This ring contains two *cis*- and one *trans*-double bond, as well as a vicinal diol. Sarains A-C

differ in the size of the second macrocycle, with sarains A (**7**), B (**8**) and C (**9**) bearing a 13-, 14-, and 15-membered ring respectively; sarains B (**8**) and C (**9**) also contain a (*Z*)-olefin moiety in the second macrocycle.[6]

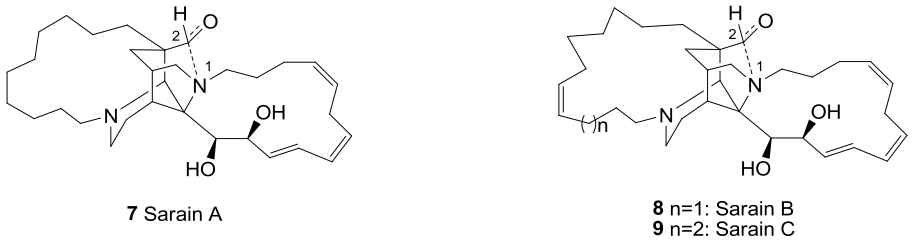


Figure 2 Sarains A-C (**7**-**9**)

Sarains A-C also exhibit an interesting zwitterionic property; that is, within the tricyclic core there is a strong 'proximity effect' between the tertiary amine (N^1) and the carbonyl (C^2=O, Figure 3).

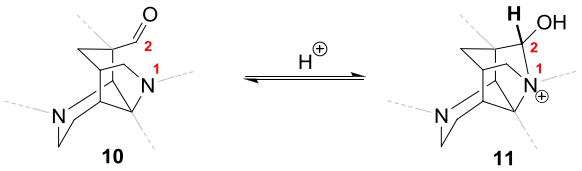


Figure 3 Proximity effect exhibited by sarains A-C

This proximity interaction has been shown to be both acid and solvent sensitive. Treatment with acid causes a disappearance of the distinctive aldehyde proton and carbon signals in the NMR spectra, and the C=O peak in its IR spectrum. Additionally, in ^{1}H and ^{13}C NMR spectra taken in CD_3COOD, the aldehyde peaks moved to 5.25 and 97.1 respectively, owing to the C-H shown in bold in tricyclic core **11** (Figure 3).[5,6,7]

1.2 Properties of the sarain alkaloids

Preliminary screenings of the biological activity of the sarains have indicated that they possess moderate antibacterial, antitumour and insecticidal properties.[8] Sarains 1-3 (**1**-**3**, Figure 1) demonstrated stronger biological activity than sarains A-C (**7**-**9**, Figure 2) when studied individually; however, both were less active than the crude extract from the *Reniera sarai* sponge itself. This increased activity could either be a consequence of a synergistic effect of the group of sarains, or there may be a minor metabolite that has not been isolated to date which possesses high biological activity. It should be noted

however that the activities of sarains A-C (**7**-**9**, Figure 2) may be influenced by pH, due to the proximity effect that was discussed in section 1.1.

1.3 Biosynthesis

Two different proposals for the biosynthetic origin of sarain A (**7**) have been published. The first of these was made by Marazano *et al*. in 1995; the proposed biosyntheses of manzamine A and keramaphidin B (natural products that have related biosynthetic origins to sarain A (**7**)) that were previously put forward by Baldwin *et al*. were important in helping Marazano and co-workers devise their biosynthetic proposal for sarain A (**7**, Figure 4). [9,10]

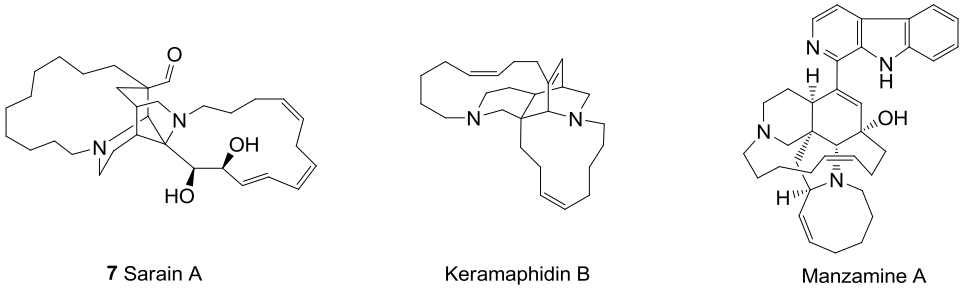
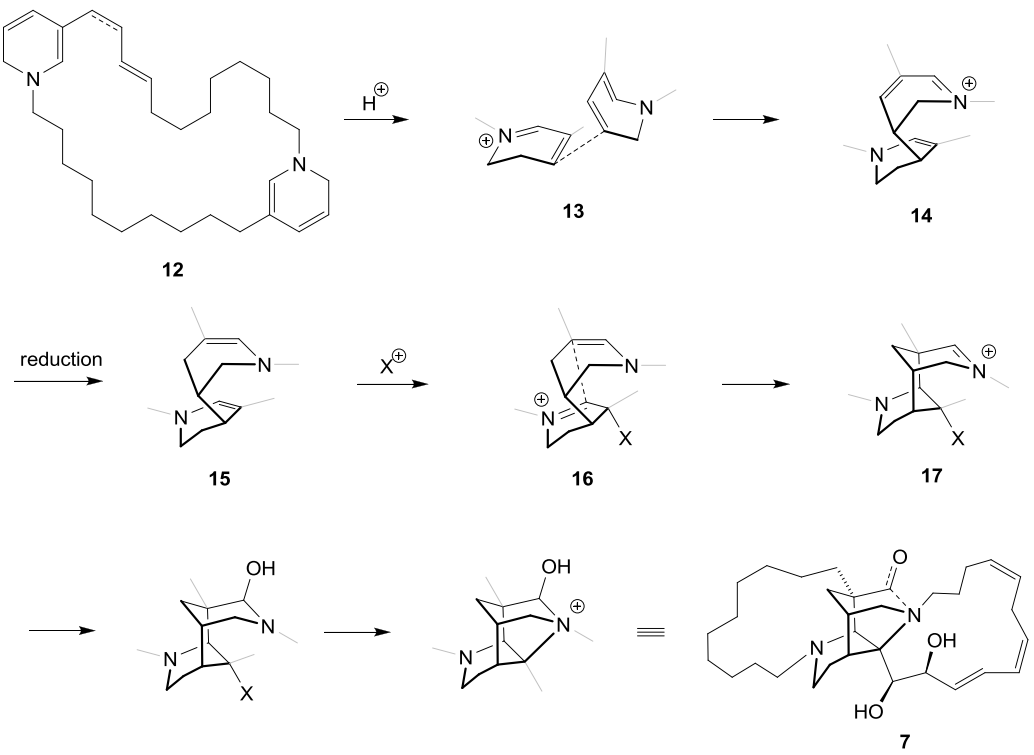


Figure 4 Structure of related marine alkaloids

The proposed biosynthetic pathway begins with macrocycle **12**, which upon protonation gives iminium species **13** (Scheme 1 – the linking chains have been omitted for clarity).[11] An intramolecular cyclisation then occurs to afford **14**, which is reduced to give enamine **15**; reaction with an electrophile such as Br^+ would then result in formation of iminium ion **16**, which can undergo intramolecular cyclisation once more to yield tricycle **17**. Final hydrolysis of the iminium in product **17**, followed by intramolecular attack of the tertiary amine onto the bromide gives the core skeleton found in sarains A-C.



Scheme 1 First possible biosynthetic pathway towards sarain A

It is also worth noting that the aforementioned biosynthetic proposal can be used to explain the biosynthesis of sarain 2 (**2**), as upon cleavage of C-C linkages in the two molecules, it is clear that its skeleton shows similarities with that of sarain A - notably a 10-membered alkyl chain (Figure 5, red).[7]

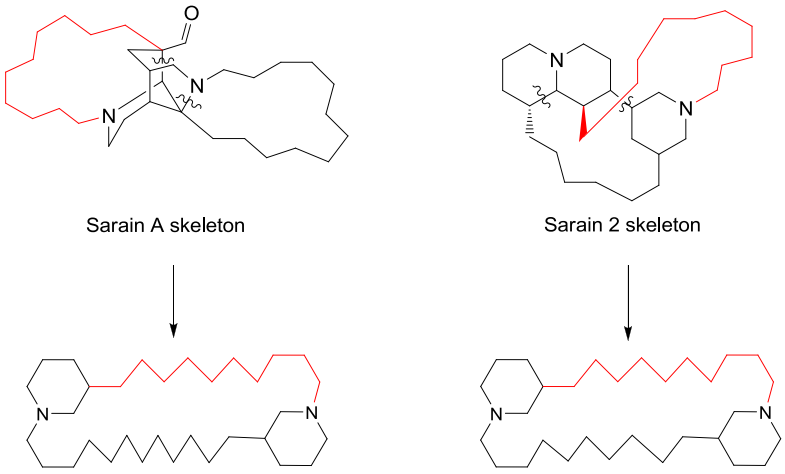
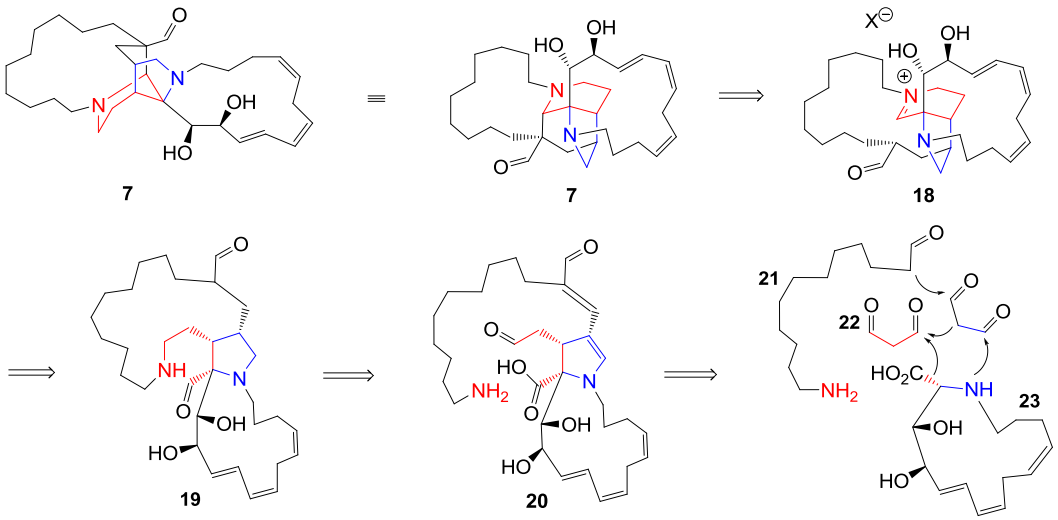


Figure 5 Biogenetic hypothesis correlating the alkaloid skeleton of sarain A to sarain 2

The second biosynthetic explanation for sarain A was also proposed by Marazano *et al.* a decade later in 2005, after model experiments that were carried out in their laboratory (Scheme 2).[12]



Scheme 2 Second possible biosynthetic pathway towards sarain A

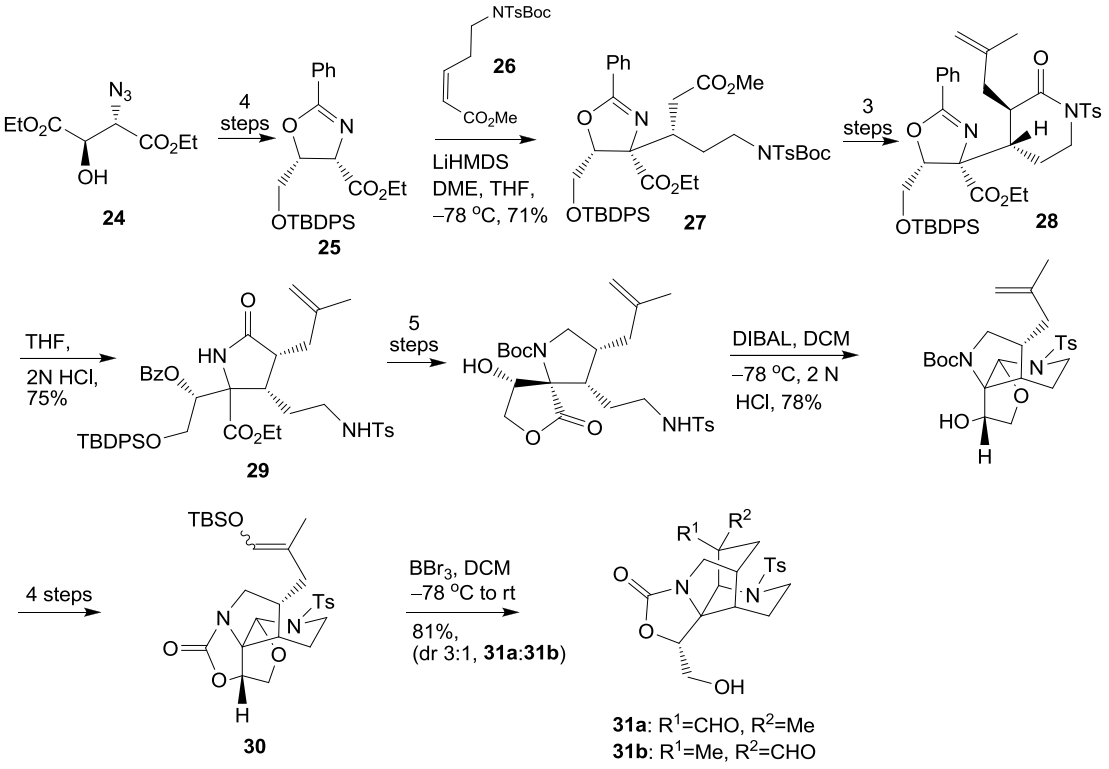
The first step in this retrobiosynthetic analysis is a retro-Mannich process which leads back to iminium ion **18** from sarain A (**7**); hydrolysis then gives secondary amine **19**. Secondary amine **19** can be accessed from primary amine **20**, whereby the forward reaction involves condensation of the primary amine and aldehyde, and reduction of an imine, enone and a carboxylic acid. Finally, primary amine **20** can be formed by condensation of macrocycle **23** and aldehyde **21** with two malondialdehyde (**22**) units.

1.4 Synthetic background

Due to the unique complex structure of sarain A, many groups have embarked upon its challenging synthesis since its isolation. The most challenging domain of sarain A to synthesise is arguably its tricyclic core; to date, 6 groups have accomplished its synthesis, with the first being by Weinreb *et al.* in 1991.[13] Out of this collection of syntheses, two have been asymmetric approaches (Overman[14] and Huang[15]) and the only total synthesis of sarain A was accomplished by Overman *et al.* in 2006.[16] This section will give a brief overview of all the successful approaches made towards both the core and the complete structure of sarain A. To begin with, Overman's asymmetric total synthesis will be reviewed.

1.4.1 Overman's asymmetric total synthesis

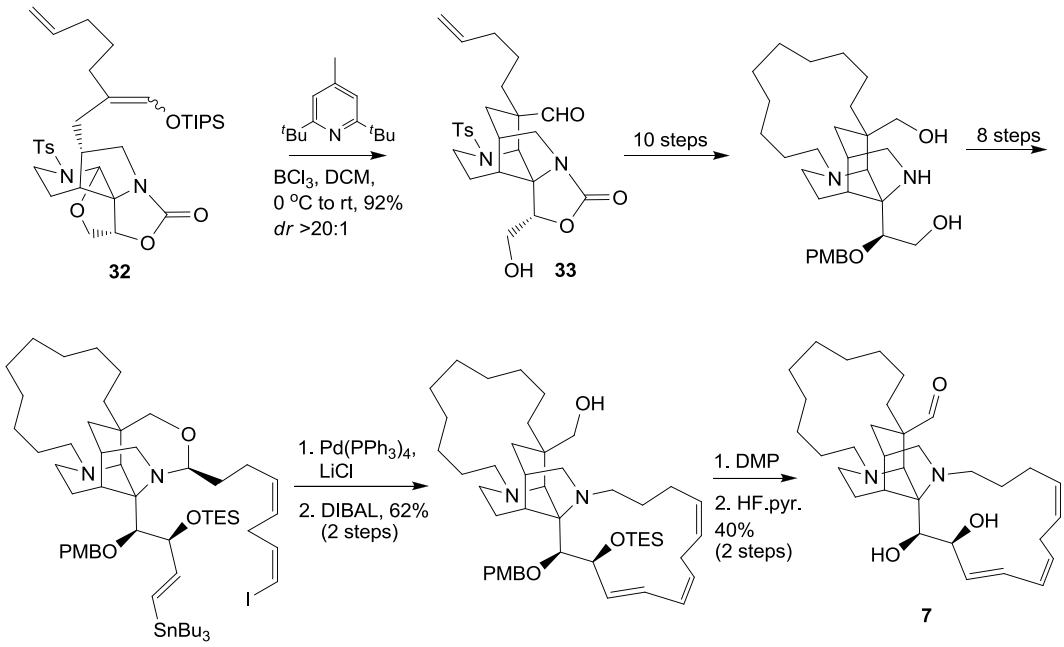
In 1998, Overman and co-workers became the first group to complete an asymmetric synthesis of the sarain A core (Scheme 3).[14] The synthesis began with conversion of azide **24** into oxazoline **25** in 4 steps. Following this, a key intermolecular Michael addition reaction between oxazoline **25** and (*Z*)-enoate **26** under optimised conditions (–78 ºC in DME:THF 2:1) gave Michael adduct **27** as a single stereoisomer; conversion into the lactam and subsequent alkylation gave lactam **28**, which upon treatment with acid underwent cleavage of the oxazoline ring and translactamisation to provide lactam **29**. Elaboration of **29** to give tetracycle **30** was achieved in 10 further steps. To generate the core, tetracycle **30** was treated with 3.5 equivalents of BBr_3 in dichloromethane, which promoted an *N*-tosyliminium ion-enoxysilane cyclisation to give core **31** as two diastereoisomers in a 3:1 ratio of **31a**:**31b** (**31b** is the desired diastereoisomer).



Scheme 3 Overman's first asymmetric synthesis of the sarain core

Overman has since improved on the diastereomeric ratio for the final cyclisation step; to achieve this, the methyl group of the side chain was replaced with a pent-4-enyl group (**32**, Scheme 4).[16] This side chain served two functions: firstly, its increased bulk

sterically promotes cyclisation to the desired diastereoisomer (the dr increases from 3:1(desired) to >1:20(desired)) and secondly it enables rapid and simple synthesis of the western macrocycle of sarain A in subsequent steps.



Scheme 4 Latter steps towards (–)-sarain A

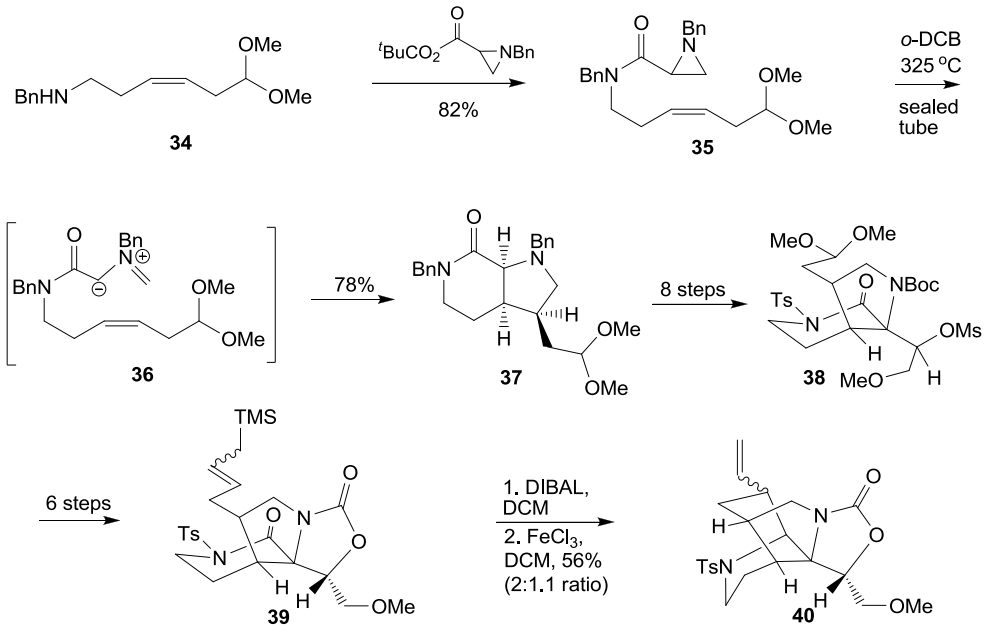
It was believed that the cyclisation proceded via the (*E*)-OTIPS enol ether as opposed to a boron enol or enolate; this is why a pyridine buffer was added in this step – to prevent the O–Si bond from breaking before cyclisation and to promote double bond isomerisation to the (*E*)-isomer at higher temperatures. [16,17,18]

Following cyclisation to core **33**, the western saturated macrocycle was made using ring closing metathesis as the key step and the eastern macrocycle was formed using Stille chemistry; completion of these two rings, along with functional and protecting group manipulation, led to completion of the first total synthesis of (–)-sarain A (**7**) in 2006.

1.4.2 Weinreb's synthesis of the core

The Weinreb group first synthesised the sarain core in 1991;[13] since that date, many improvements to the route towards the core were made so that the eastern and western macrocycles of sarain A could be attached onto the core after its synthesis.[19,20,21] In Weinreb's most recently published route (Scheme 5), aziridine **35** (which was formed

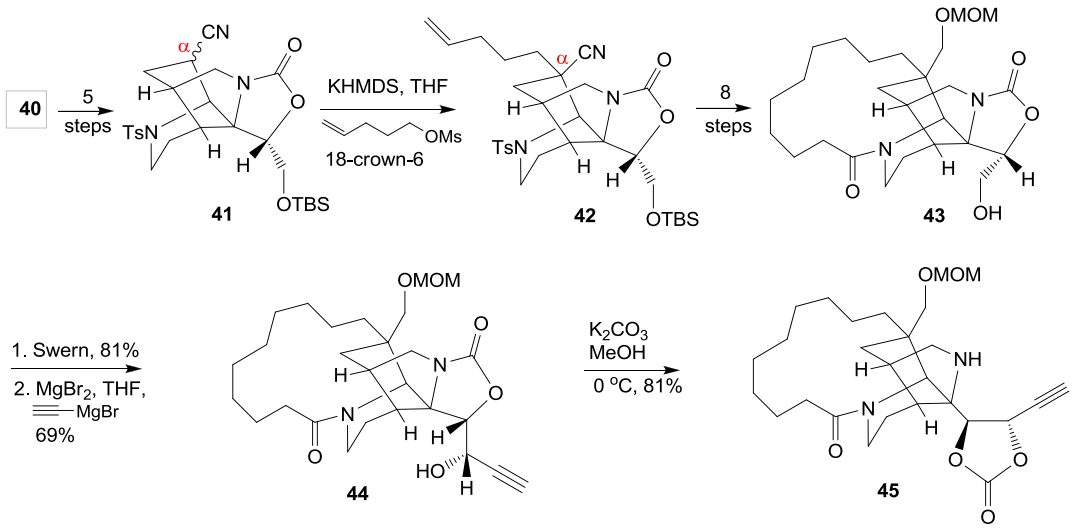
from amine **34** in 82% yield) underwent a stereospecific [3+2] cycloaddition via azomethine ylide **36** to form bicycle **37** in good yield.



Scheme 5 Weinreb's synthesis of the core

A series of relatively straightforward steps that achieve the introduction of a protected diol onto the ring junction and protecting group manipulation were next implemented on bicycle **37** to give bicycle **38**; this was converted into allylsilane **39** in 6 steps. DIBAL reduction of the amide moiety in **39** and subsequent treatment with $FeCl_3$ promoted the crucial allylsilane/*N*-sulfonyliminium ion cyclisation to give rise to sarain core **40** as a mixture of epimers.

Weinreb's latest progress towards the complete structure of sarain A includes conversion of core **40** into nitrile **41** in five steps; these steps include a protecting group exchange and functionalisation at C^{α} (Scheme 6).[21] The final step in this sequence involved deprotonation at C^{α}, followed by a stereoselective alkylation (attack from the alkylating agent is from the least hindered equatorial position) and hence the mixture of epimers of **41** obtained is not detrimental to the synthesis. A further 8 steps result in the completion of the western macrocycle to give rise to **43**.

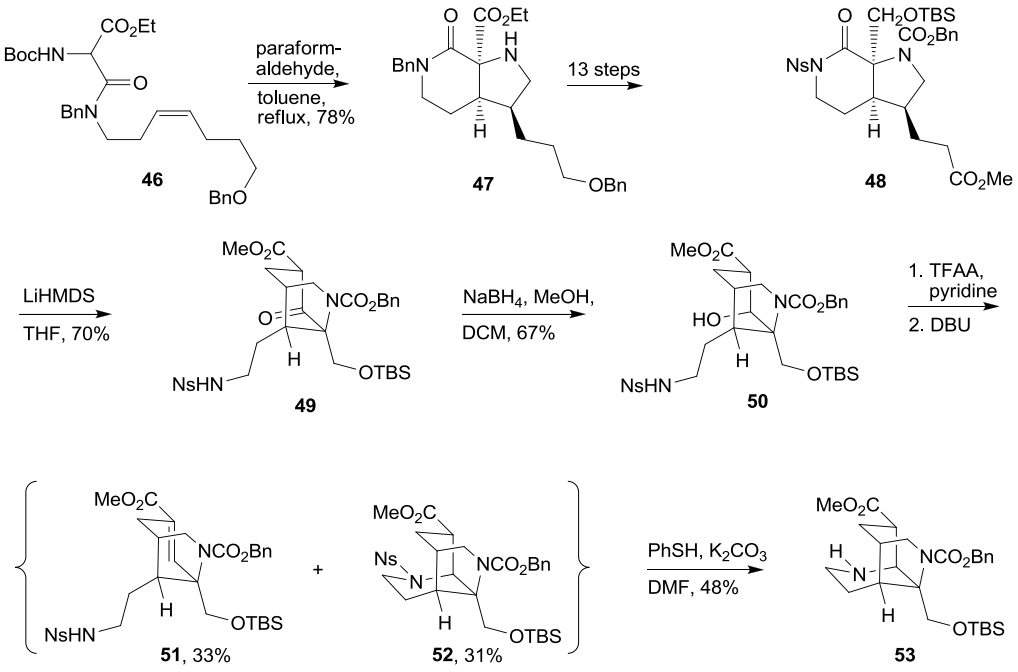


Scheme 6 Weinreb's latter steps towards the complete synthesis of sarain A

The final few steps that have been published involve a Swern oxidation of the alcohol in **43** and subsequent attack from ethynylmagnesium bromide to give alcohol **44**; upon treatment of **44** with K_2CO_3 in MeOH, carbonate **45** is formed. This compound contains the final two stereocentres of the eastern macrocycle and also a secondary amine that may help to complete the synthesis of the final part of the remaining ring.

1.4.3 Heathcock's synthesis of the core

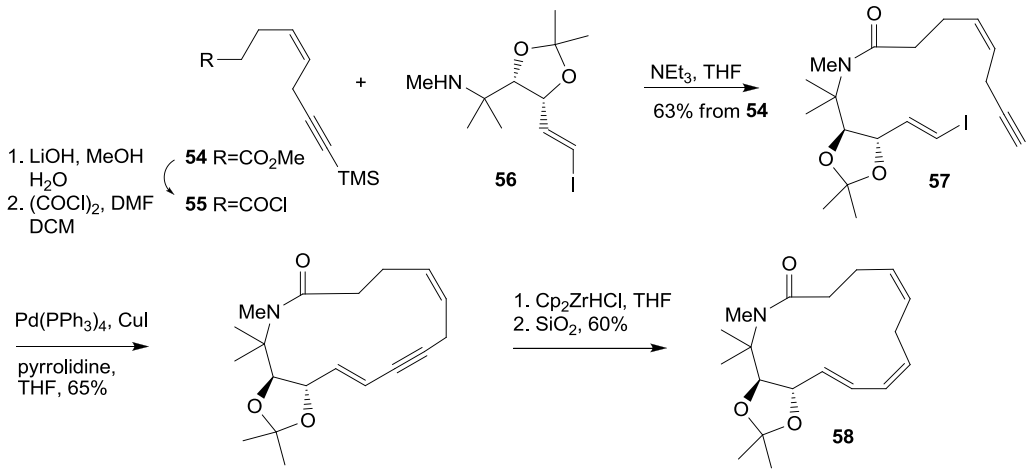
Heathcock's approach to the sarain core (Scheme 7) employs an azomethine ylide cyclisation similar to that used in Weinreb's synthesis of the core (Scheme 5);[22] the intermediate azomethine ylide was formed using a procedure described by Grigg and co-workers whereby α-amino acid derivative **46** is condensed with paraformaldehyde.[23] Following cyclisation, bicycle **47** was obtained in 78% yield; after some lengthy protecting group manipulation, bicycle **48** was obtained and then treated with LiHMDS to promote clean isomerisation to β-ketoester **49**.



Scheme 7 Heathcock's synthesis of the sarain core

Reduction of ketone **49** to alcohol **50**, followed by dehydration and treatment with a base, resulted in a mixture of desired tricycle **52** and α,β-unsaturated ester **51**. Treatment of the mixture of **51** and **52** with thiophenol and potassium carbonate in dimethylformamide successfully removed the nosyl group from tricycle **52** to give sarain core **53**.

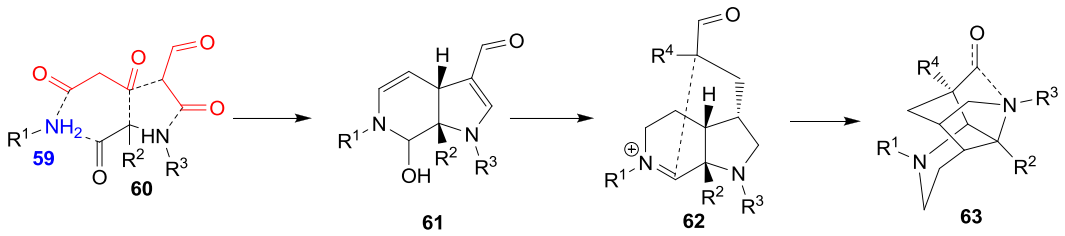
Heathcock was the first to devise a synthetic route towards the eastern macrocycle of sarain A (Scheme 8).[24] The synthesis started with conversion of ester **54** into acid chloride **55**, which was then coupled with amine **56** to give amide **57** containing the two stereocentres of the eastern macrocycle. Following this, a Sonogashira coupling closed the ring and hydrozirconation followed by exposure to wet silica gel afforded desired macrocycle **58**.



Scheme 8 Heathcock's synthesis of the eastern macrocycle of sarain A

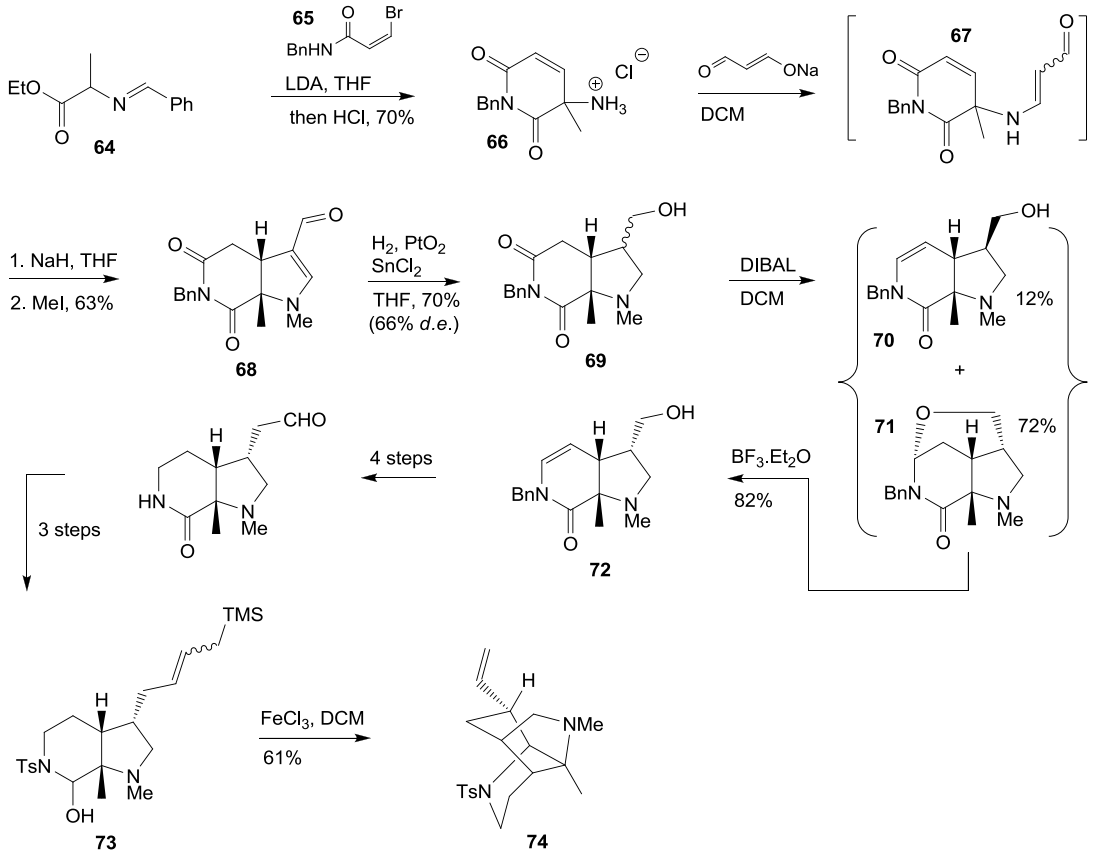
1.4.4 Marazano's synthesis of the core

Marazano's approach towards the core mimics his biosynthetic proposal (see Scheme 2); in this proposal (Scheme 9), 4 molecules (**59**, **60** and two malonaldehyde units - red) are condensed to form bicycle **61**.[25] The following steps include reduction of the side chain aldehyde, elongation and a ring closure of **62** to make core **63**.



Scheme 9 General biosynthetic strategy towards core

Hence, the route taken by Marazano began with deprotonation of alanine derivative **64** and treatment with bromoacrylamide **65**, followed by acidic imine hydrolysis to give salt **66**. Salt **66** was then mixed with the sodium salt of malonaldehyde to form intermediate **67**, which, when treated directly with sodium hydride and iodomethane gave bicycle **68** in 63% yield.



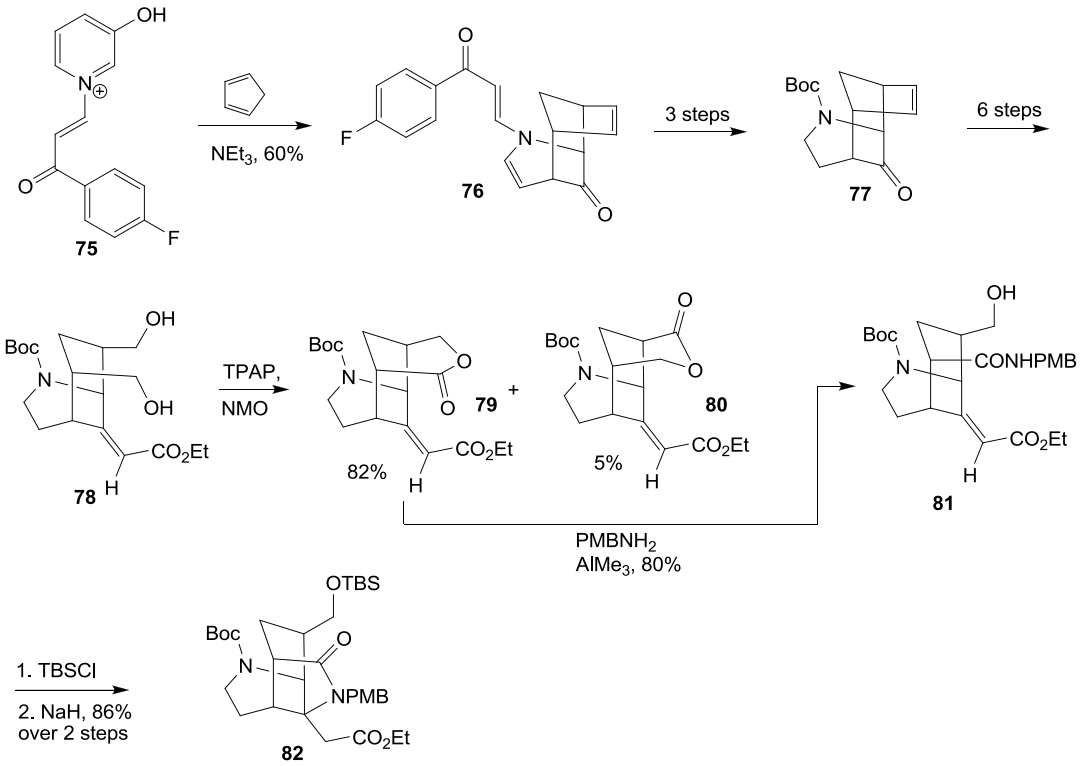
Scheme 10 Marazano's synthesis of the core

The enal moiety of bicycle **68** was reduced using hydrogenation in the presence of platinum oxide and tin dichloride to give alcohol **69** with mediocre diastereoselectivity. However, reduction of the crude mixture of **69** with DIBAL gave two products **70** and **71**, with the major product **71** containing the correct stereochemistry at the newly formed chiral centre. This sequence was followed by treatment of **71** with $BF_3.Et_2O$ to give cyclic enamine **72**, which was converted into target precursor **73** in 7 steps. Finally, in a similar fashion to that employed by Weinreb (Scheme 5), reaction of precursor **73** with ferric chloride promoted the key cyclisation to give sarain core **74** in a reasonable yield.

1.4.5 Cha's synthesis of the core

The Cha synthesis of the sarain core is the shortest reported to date (Scheme 11). The synthesis began with a [4+3] cycloaddition between pyridinium salt **75** and cyclopentadiene to give cyclisation product **76** in 60% yield.[26,27] The following 3 steps served to exchange the protecting group, giving *N*-Boc-compound **77**. A series of simple steps then converted **77** into diol **78**, which upon treatment with TPAP and NMO

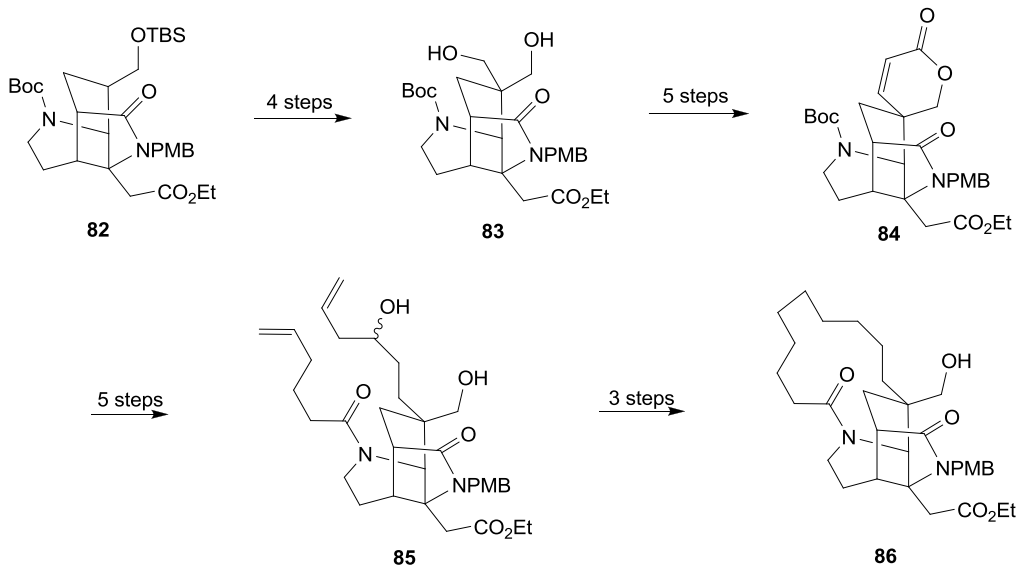
underwent oxidation to form lactone **79**, along with a small amount of lactone **80**. The good selectivity achieved is thought to be a consequence of the two diol units in **78** experiencing different steric interactions with the (*Z*)-α,β-unsaturated ester.



Scheme 11 Cha's synthesis of the sarain core

Lactone **79** was subsequently opened to give **81** and the resulting alcohol protected; deprotonation using sodium hydride promoted an intramolecular Michael addition to give sarain core **82**.

Cha has also formed the western macrocycle of sarain A (Scheme 12); to achieve this, core **82** was initially converted into diol **83** in 4 steps. The following five steps, one of which was an intramolecular Horner-Wadsworth-Emmons reaction, provided lactone **84**.

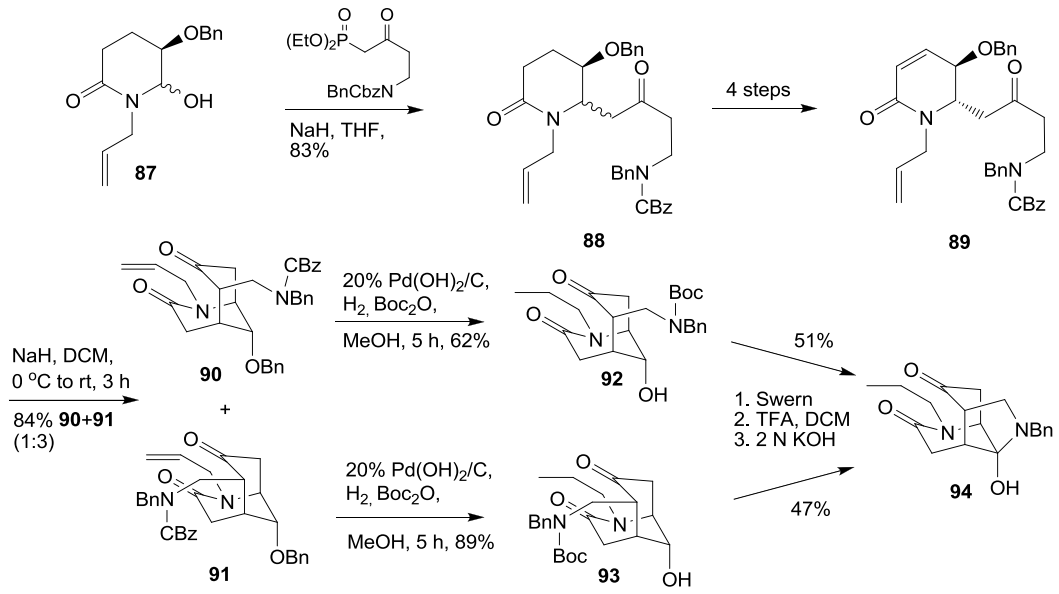


Scheme 12 Cha's assembly of the western macrocycle of sarain A

Incorporation of the two side chain olefins onto the core framework, followed by ring closing metathesis, dehydration and a final reduction, provided desired compound **86**. Cha has also synthesised a compound analogous to **86**, only instead of a PMB protecting group on the nitrogen atom, it contains a $(CH_2)_4OPMB$ group; this increase in chain length should make formation of the eastern macrocycle achievable.[26]

1.4.6 Huang's asymmetric synthesis of the core

In Huang's recent asymmetric synthesis of the core (Scheme 13), lactam **87** undergoes a tandem Horner-Wadsworth-Emmons-aza-Michael reaction to give rise to lactam **88** in 83% yield as a 3.1:1 mixture of *trans*- to *cis*-isomers.[15] Lactam **88** is then converted into enone **89** in 4 steps, which, upon treatment with sodium hydride, undergoes a Michael addition to yield bicycle **90**/**91** as a 1:3 mixture of diastereoisomers respectively.



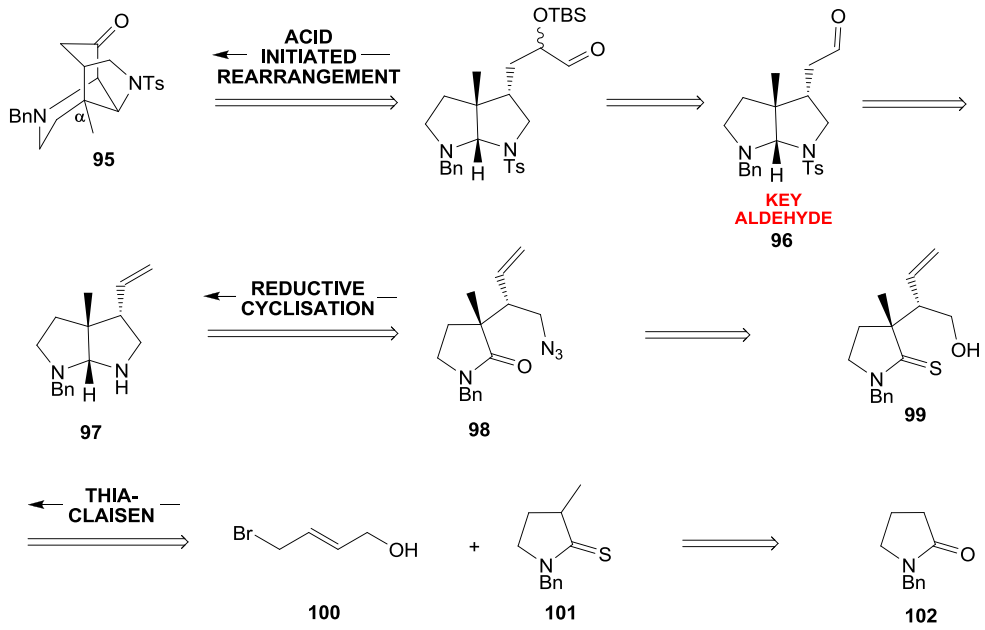
Scheme 13 Huang's asymmetric synthesis of the sarain core

Fortunately, Huang and co-workers were able to convert both diastereoisomers **90**/**91** into core **94** via precursors **92** and **93**. This was achieved by removal of the *O*-benzyl protecting group to give **92**/**93**, Swern oxidation, removal of the Boc-protecting group and workup of the product with KOH (to promote the final cyclisation and cause epimerisation of **93**).

1.4.7 Porter's approaches towards the core

1.4.7.1 Retrosynthesis - synthesis of key aldehyde intermediate

A number of different strategies towards the sarain core have been adopted by the Porter group; all of these go via key aldehyde **96** (Scheme 14). At this stage there are many pathways that have been taken in order to convert this molecule into sarain core **95**, and the results from these will be discussed later in this section.[28]



Scheme 14 Porter's retrosynthesis of the sarain core*

The bicyclic part of aldehyde **96** is initially formed by the reductive cyclisation of azide/lactam **98** into bicycle **97**; this reaction is achieved by treatment of azide/lactam **98** with tri-*n*-butylphosphine to give the corresponding iminophosphorane, followed by treatment with lithium aluminium hydride to effect cyclisation.[28]

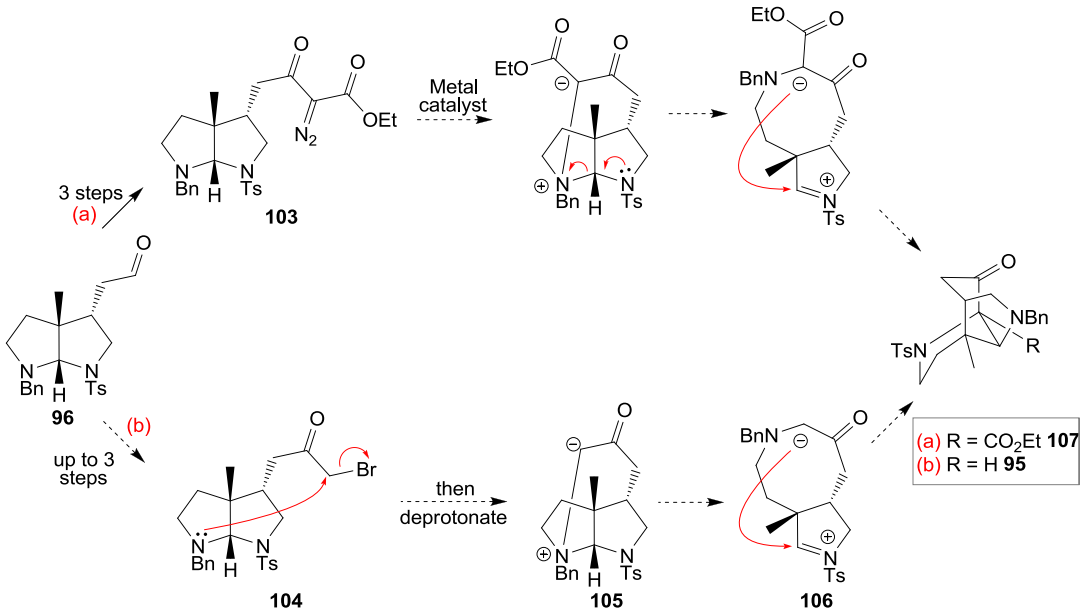
Another vital step is the thia-Claisen rearrangement that sets the correct relative stereochemistry of two stereogenic centres in thiolactam **99**. The precursor to this rearrangement is formed upon alkylation of thiolactam **101** with bromide **100**, followed by heating to 40 ºC; deprotonation using triethylamine then promotes the [3,3]-sigmatropic rearrangement.[28]

1.4.7.2 Attempted transformations of key aldehyde into the sarain core

Members of the Porter group had initially aimed to access the sarain core from aldehyde **96** using a novel metal-catalysed ammonium ylide rearrangement (path a, Scheme 15). The required diazoester **103** was made in 3 steps from aldehyde **96**, but unfortunately, the desired rearrangement did not occur despite attempts with a range of catalysts in different solvents; a complex mixture of products was obtained in all cases, with no

* The methyl group at C^{α} is not part of the sarain core; however, it had to be added into Porter's synthesis at an early stage to prevent isomerisation of bicycle **97** (and subsequent structures) during purification. Without the methyl group in this position, it was difficult to maintain stereochemical purity.

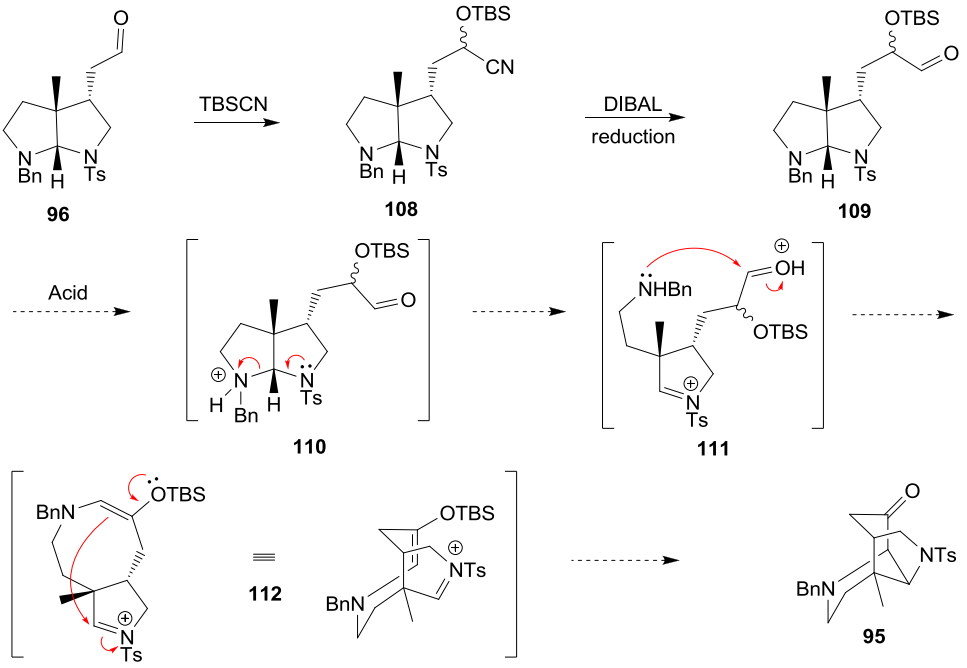
indication for the formation of sarain core **107**.[29]



Scheme 15 Rearrangement attempts towards the sarain core

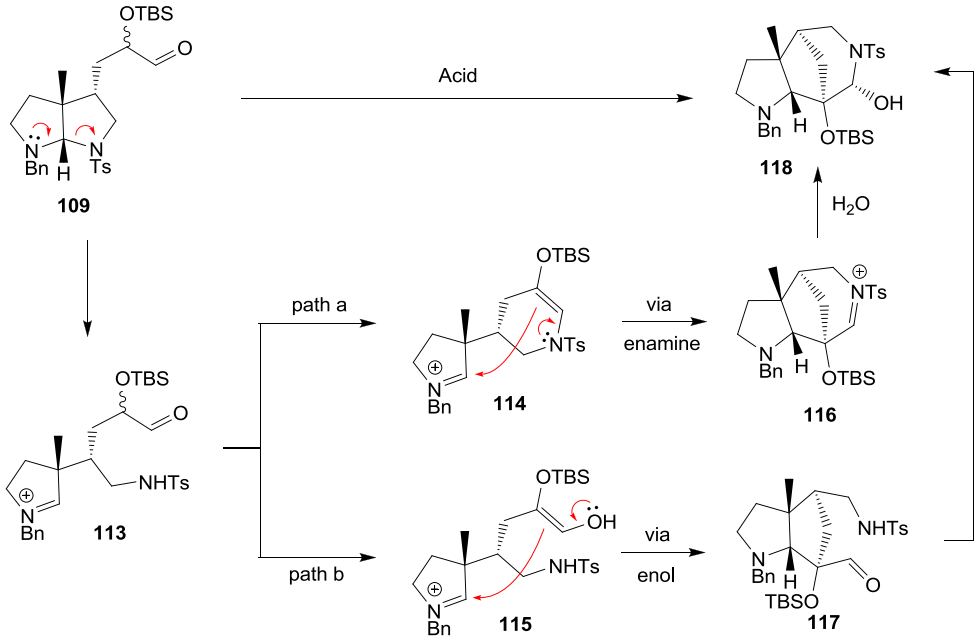
Attention was next turned to a similar rearrangement that could enable the formation of sarain core **95**. In this case, intramolecular *N*-alkylation by reaction with the nearby bromide in **104** would occur first, and, following deprotonation, bicycle **105** would ring open and then close to form target tricycle **95** via **106**.[29] However, the synthesis of bromide **104** was not possible and hence the proposed rearrangement could not be investigated.

The final major attempt made within the group was an acid initiated rearrangement of aldehyde **109**, which itself was synthesised in two steps from key aldehyde **96** (Scheme 16).[28] Upon protonation of the more basic nitrogen atom in aldehyde **109** to give **110**, spontaneous ring opening of the bicyclic aminal was expected to give rise to amine **111**, which, after condensation with the aldehyde, would form silyl enol ether **112**; this would then attack the iminium ion and form sarain core **95**.



Scheme 16 Acid-catalysed route towards the sarain core

When aldehyde **109** was treated with a range of acids, the desired product was not observed; instead, decomposition of the starting material or recovery of starting material resulted in most cases. However, when aldehyde **109** was subjected to acetic acid and methanol at 60 ºC, tricycle **118** was isolated as the main product (Scheme 17).



Scheme 17 Acid catalysed rearrangement to form 5,7-tricycle **118**

It is believed that tricycle **118** resulted from initial ring opening of the bicyclic aminal in aldehyde **109** in the undesired direction; the reaction could then take one of two pathways to give the product. Firstly, condensation of the sulfonamide with the aldehyde, followed by subsequent attack from the enamine generated and trapping of the iminium ion with water would generate tricycle **118** via iminium ion **116** (path a, Scheme 17). Alternatively, enolisation of aldehyde **113** followed by attack onto the iminium ion from the enol in **115** and subsequent reaction between the amine and the aldehyde in **117** would yield the same product, **118** (path b, Scheme 17).

The mode of aminal opening can be explained by the fact that the more nucleophilic nitrogen atom supplies the electron push to encourage ring opening. However, under acidic conditions, one would expect the same nitrogen (i.e. the more nucleophilic one) to become protonated, and hence ring opening to occur in the opposite direction to that observed. The observation of **118** as the major product suggests that, under these conditions, aminal opening occurs without initial protonation of a nitrogen atom.

1.5 [3,3]-Sigmatropic rearrangements

As explained in section 1.4.7, a thia-Claisen rearrangement had been used to establish the correct relative stereochemistry in precursors to the sarain core. The products obtained from these rearrangements are racemic, and, as a result, it would be desirable to replace this with an asymmetric variant. The following section will discuss the Claisen and thia-Claisen rearrangements, followed by a discussion of asymmetric versions that can be found in the literature.

1.5.1 Claisen rearrangement

The Claisen rearrangement is a [3,3]-sigmatropic rearrangement of allyl vinyl ethers **119** that provides a method for the generation of γ,δ-unsaturated carbonyl compounds (**120**, Scheme 18); this rearrangement provides a mild and effective way to form C-C bonds and is also a reliable way to generate tertiary and quaternary carbon centres.[30] The first example of this reaction was published by Ludwig Claisen in 1912; his original work focused on the reorganisation of allyl phenyl ether (**121**, Scheme 18) into rearranged product **122**.[31] Although this rearrangement involves an aromatic compound, the Claisen rearrangement has since been extended to and applied to aliphatic variants.

Scheme 18 The Claisen rearrangement (left) and [3,3] rearrangement of allyl phenyl ether **121** (right)

1.5.1.1 Mechanistic features

There are two feasible geometries that the transition states generated in Claisen rearrangements can adopt: (i) chair-like (**123**, Figure 6) and (ii) boat-like (**124**, Figure 6).[30] Both of these transition states are fully suprafacial [π_2s + σ_2s + π_2s] processes and hence, according to the Woodward-Hoffman rules,[32] are thermally allowed.

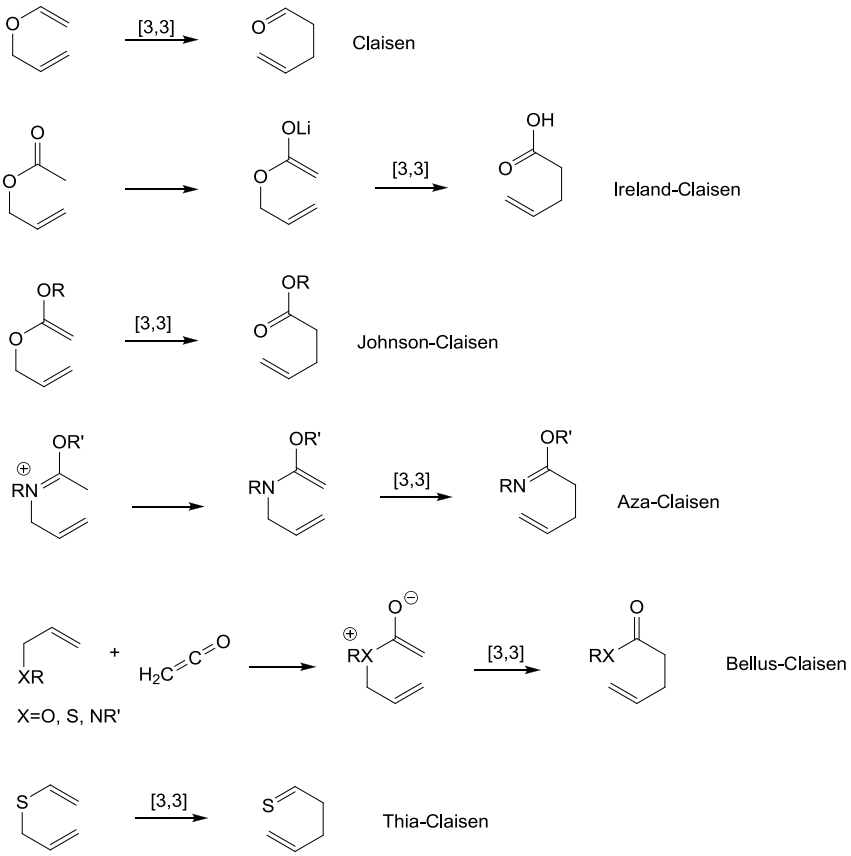
Figure 6 Chair- (**123**) and boat-like (**124**) transition state conformations in Claisen rearrangements

It has become generally accepted that the chair-like conformation is lower in energy and therefore most likely. Despite this, work is still going on today in many research groups to find the precise nature and geometry of the transition state involved in this process.[33,34,35,36,37,38]

The chair-like transition states are typically highly ordered and repulsive interactions are minimised by placing bulky groups in pseudo-equatorial positions; when this is combined with well defined olefin geometries, the stereochemistry of the product can be easily predicted.

Since its discovery in 1912, many variations of the Claisen rearrangement have been developed, these include: (i) the Ireland-Claisen rearrangement of silyl ketene acetals derived from allyl esters, (ii) the Johnson-Claisen rearrangement of ketene acetals generated from allylic alcohols and orthoesters, (iii) the aza-Claisen rearrangement of ketene *O*,*N*-acetals, (iv) the Belluš-Claisen rearrangement of γ,δ-unsaturated esters, amides and thioesters generated from reaction of allylic ethers, amines and thioethers with ketenes and (v) the thia-Claisen rearrangement, which is the sulfur analogue of the

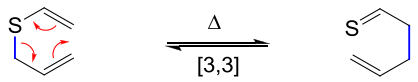
Claisen rearrangement (Scheme 19). This thesis will focus on the thia-Claisen rearrangement.



Scheme 19 – Simplified view of the Claisen-type rearrangement family

1.5.2 Thia-Claisen rearrangement

The thia-Claisen rearrangement is the sulfur analogue of the Claisen rearrangement (Scheme 20). It was first reported in 1962 when Hackett *et al***.** carried out work on allyl aryl sulfides;[39] it has been used on a number of occasions in the total synthesis of natural products.[40,41,42,43,44]



Scheme 20 The thia-Claisen rearrangement

In contrast to its oxygen analogue, the thia-Claisen rearrangement of *S*-allyl thiophenols generally requires higher temperatures and products can be unstable, making them difficult to isolate. On the other hand, the aliphatic version proceeds under milder conditions, making it more easily applicable in synthesis.

Analogous to the Claisen rearrangement, the thia-Claisen rearrangement is believed to go through a chair-like transition state. The mechanistic details of thia-Claisen rearrangements are the subject of current research.[45]

1.5.3 Stereoselective [3,3]-rearrangements

A consequence of the highly ordered transition state of Claisen-type rearrangements, in combination with well-defined olefin geometries in the starting material, is that chirality transfer from a stereogenic centre is generally excellent. Two approaches have been developed to induce chiral information transfer in such rearrangements: (i) intra-annularly; (ii) extra-annularly (Figure 7). The intra-annular approach involves the stereogenic part being incorporated *into* the cyclic framework of the transition state. Thus, in this process, the chiral information in the six centres that are reorganised during the [3,3]-sigmatropic rearrangement is transferred in a concise and predictable fashion to give the product with good selectivity. There are four main factors that influence intra-annular diastereoselectivity: (i) transition-state geometry, (ii) vinyl double bond geometry, (iii) allyl double bond geometry and (iv) the substituent at C^4. This type of stereocontrolled Claisen rearrangement has been extensively reviewed.[30]

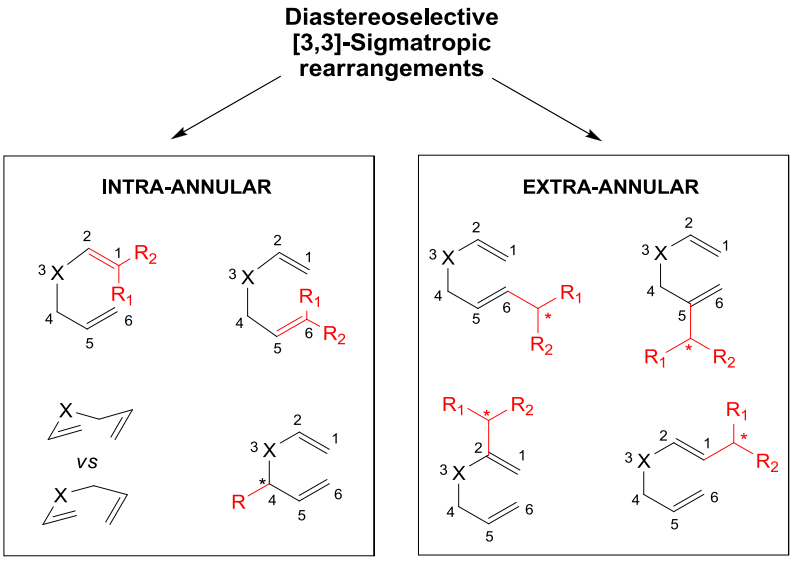


Figure 7 Types of diastereoselective control methods in [3,3]-rearrangements

The extra-annular process is one in which the inducing chiral centre is incorporated *outside* the transition state framework and is generally more difficult to achieve than intra-annular induction. Four types of extra-annular stereocontrol methods can be

envisaged; the external stereogenic centre can be attached either to the allyl fragment (at C^5 or C^6) or the vinyl fragment (at C^1 or C^2).

For the purpose of this work, only extra-annular control by incorporation of the chiral centre adjacent to C^6 will be considered; this type of stereocontrol has been scarcely reported in the literature.

1.5.3.1 [3,3]-Sigmatropic rearrangements directed by a stereocentre at C^6

Asymmetric thia-Claisen rearrangements normally proceed through a low energy chair conformation containing minimal 1,3-diaxial interactions. There are two important factors that affect the diastereoselectivity (see below). Although some authors tend to rationalise their results using only one of these factors as an explanation, both are very similar (they differ only by a 30º rotation about a single bond) and so it is likely that both play some part.

Factor 1: Minimise Allylic strain [#]

One factor that is important is minimising allylic strain; this is a type of strain energy resulting from the interaction between a substituent on one end of an olefin with an allylic substituent on the other. Shown in Figure 8 (top) is an (*E*)-allylic system drawn in three different orientations; each are of different energies due to the differing amounts of allylic strain present. The eclipsed conformations (**125** and **126**) are lowest in energy, with conformation **125** being lower in energy than **126** as the hydrogen atom (H*) is eclipsed with another hydrogen atom across the olefin, rather than the larger methyl group. Conformation **127** is highest in energy as the two methyl groups are staggered with the hydrogen atom (H*).

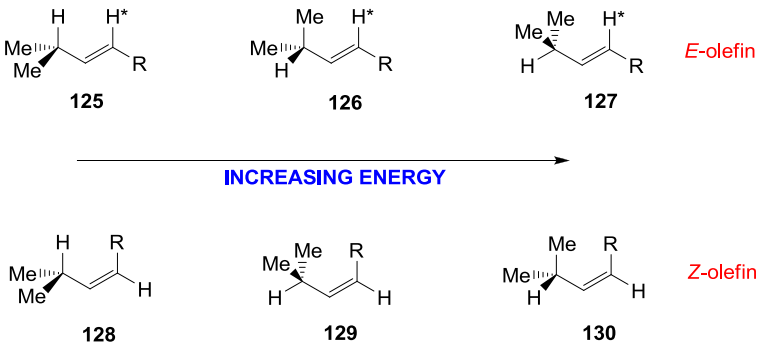


Figure 8 Allylic systems[46]

[#] This explanation does not rely on the reaction being nucleophilic, i.e. a system could adopt a conformation that has minimal allylic strain, even if it is not undergoing attack by a nucleophile.

The situation changes slightly for a (*Z*)-olefin; the highest energy orientation **130** has the methyl group eclipsed with the R-group. However conformation **128**, which has the small hydrogen atom eclipsed with the R-group, is still lowest in energy and therefore most frequently adopted.

Attack onto a double bond of an allylic system (i.e. as in a Claisen-type rearrangement) that possesses minimal allylic strain would then be expected to occur from the less hindered side (**131** and **132**, Figure 9); hence, attack from a nucleophile is from the side that is opposite to the largest group. This type of nucleophilic attack is outlined in Figure 9 along with the associated Newman projection **133**.

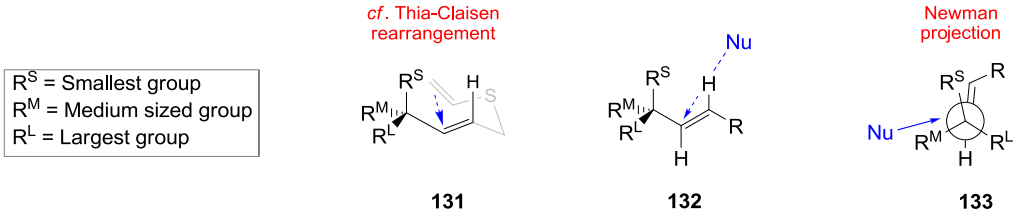


Figure 9 Nucleophilic attack on an allylic system possessing minimum allylic-strain

Factor 2: Transition state stabilisation (Houk's model)[47,48,49,50]

Houk's model (which was originally applied to nitrile oxide cycloadditions) states that when a nucleophile attacks a double bond in a cyclic transition state, the most electronegative substituent is placed perpendicular to the double bond, in the *anti* position, in order to maximise stabilisation in the transition state. The smallest group must occupy the *inside* position, which is staggered with the double bond, and the remaining group occupies the *outside* position (**136**, Figure 11). When this rule is applied to Claisen-type rearrangements, conformation **137** would result.

Placement of the most electronegative group in the *anti* position results in the newly forming σ-bond being in the correct orientation to enable stabilisation by overlap with the low-lying σ* orbital of the C–X bond (**134** and **135**, Figure 10). Such an effect, in related Ireland-Claisen rearrangements, has been characterised computationally by Kahn and Hehre as involving the *more electron-poor face of the electrophilic component*.[51] This explanation contrasts with the Felkin-Anh model for nucleophilic

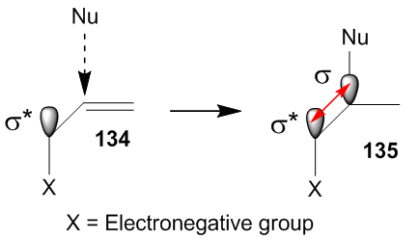


Figure 10

attack onto a carbonyl group (**138**) , which places the medium group, rather than the small group, in the *inside* position (Figure 11).[52,53,54]

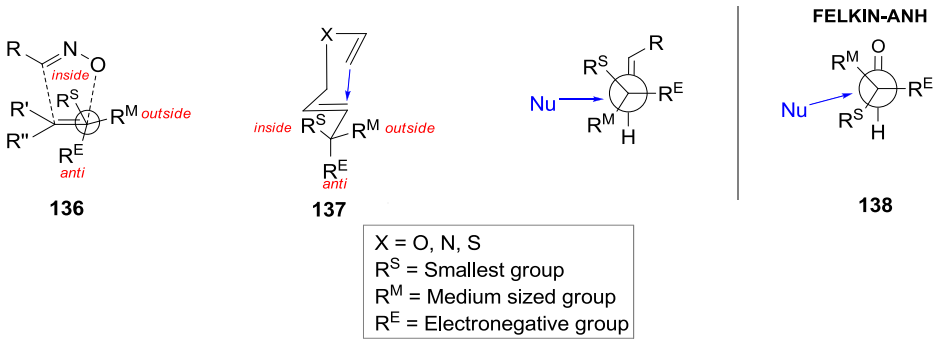
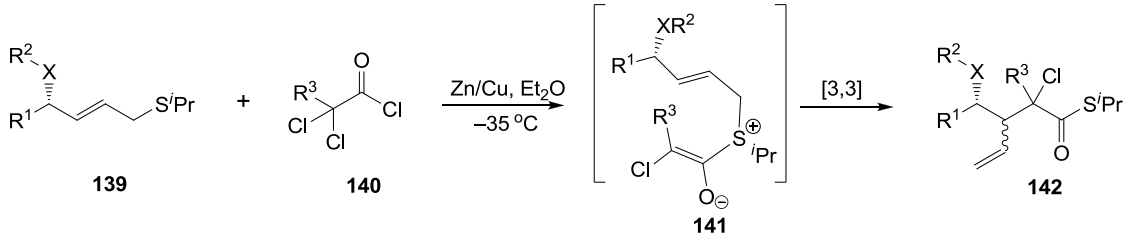


Figure 11 Houk's model for nucleophilic attack on an alkene (left) and the Felkin-Anh model (right)

1.5.3.1.1 Belluš Claisen rearrangements of allyl sulfides

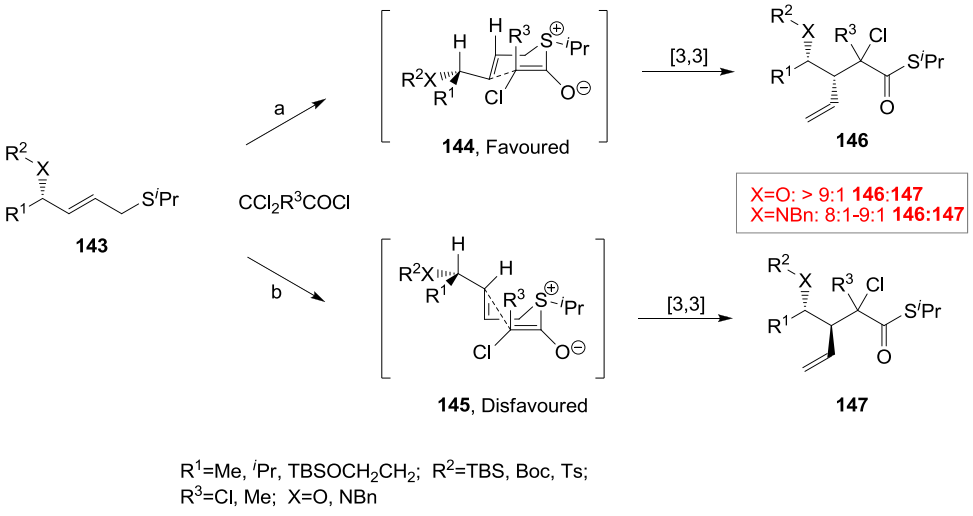
Belluš *et al.* were the first to report a highly diastereoselective [3,3]-sigmatropic rearrangement directed by a stereogenic centre at C[6].[55] In their studies, allyl sulfide **139** and an electron-deficient ketene derived from acid chloride **140** reacted to form zwitterionic intermediate **141**, which, following a ketene-Claisen rearrangement, gave thioester **142** (Scheme 21).



Scheme 21 Diastereoselective ketene-Claisen rearrangement

The reaction could be conducted at low temperature due to charge neutralisation providing a sufficient driving force - this is thought to have helped towards the high level of diastereoselectivity obtained (Scheme 22). The reaction could take one of two pathways; namely pathway a or pathway b (Scheme 22). Pathway a is the lower energy pathway due mainly to the lack of 1,3-diaxial repulsive interactions present in **144**. Conversely, pathway b goes via boat **145**, which is of higher energy as it possesses stronger 1,3-diaxial repulsive interactions.

Belluš explained the diastereoselectivity obtained using transition states **144** and **145**. Thus, with the two hydrogen atoms in **144** eclipsed across the allylic system, attack is from the less sterically encumbered face to give product **146** as the main diastereoisomer.



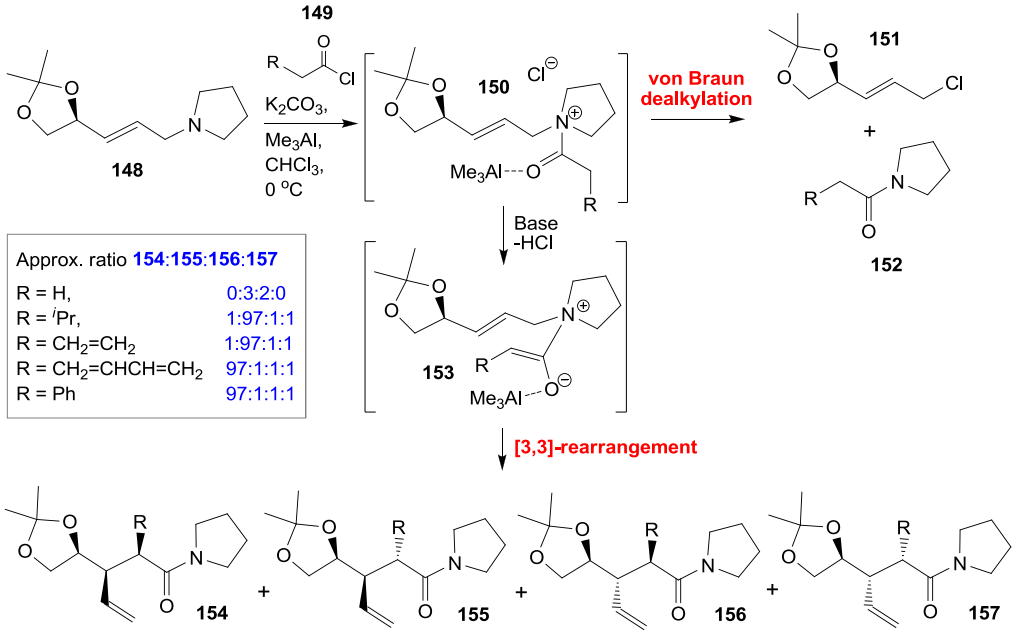
Scheme 22 Diastereoselective ketene-Claisen rearrangement

Interestingly, when XR^2=NBn, lower diastereoselectivities were obtained in the [3,3]-sigmatropic rearrangement; after performing modelling experiments on this system, the author explained the difference in diastereoselectivity as a consequence of boat conformation **145** simply being of significantly lower energy when XR^2=NBn, resulting in a reduced energy difference between the two transition states.

1.5.3.1.2 Aza-Claisen rearrangements

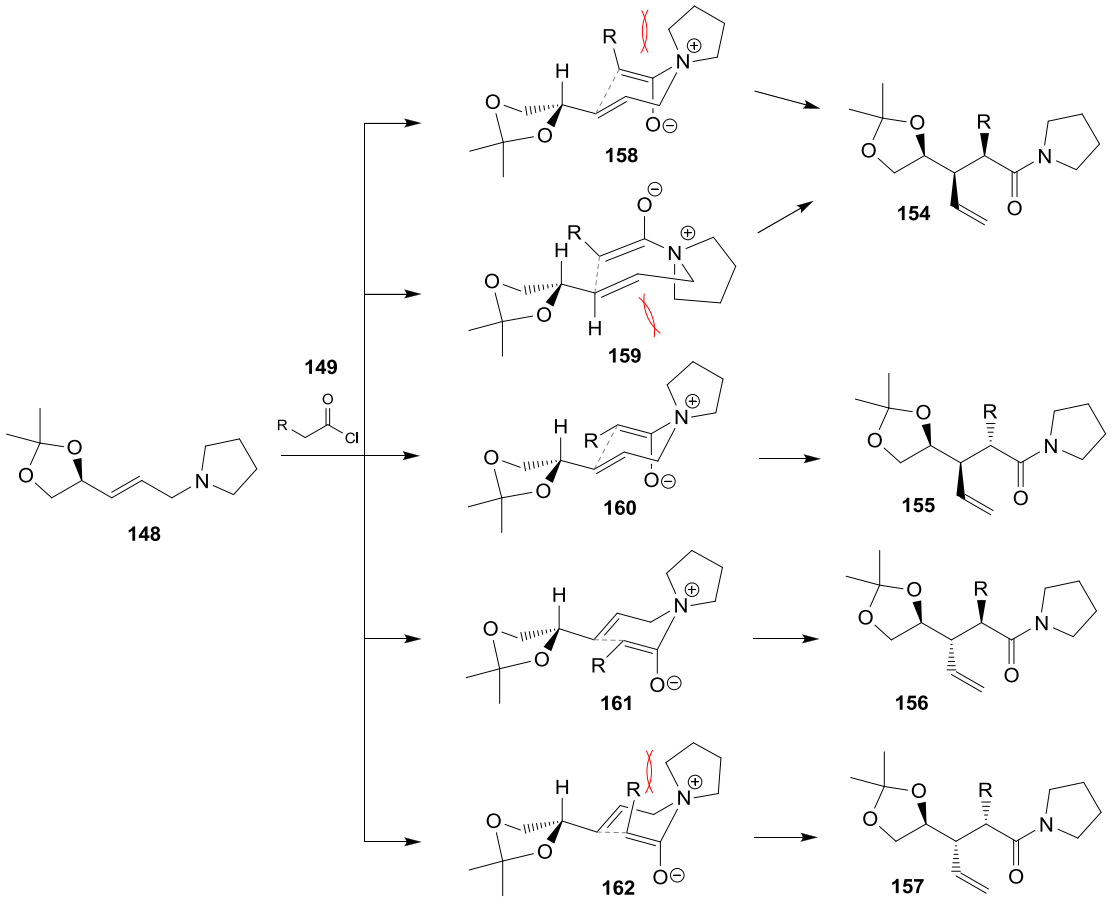
Nubbemeyer *et al*. have focused on the development of diastereoselective zwitterionic aza-Claisen rearrangements.[56,57] Unlike in the work described above on ketene-Claisen rearrangements, formation of zwitterionic intermediate **150** (Scheme 23) was not straightforward; mixing *N*-allylpyrrolidine **148** with a range of *α*,*α*-disubstituted carboxylic acid chlorides commonly resulted in a von Braun degradation, giving rise to allyl chloride **151** and the corresponding amide **152**. To make this unwanted process less likely, *N*-allylpyrrolidine **148** was treated with α-monosubstituted acid halides **149** in the presence of trimethylaluminium at low temperatures (0 ºC). These conditions enabled successful aza-Claisen rearrangements of **150** to occur to generate **154-157** as main products (Scheme 23). These products (**154-157**) are useful intermediates in total

synthesis, for example in the syntheses of (+)-dihydrocanadensolide and (–)-petasinecin.[56,57]



Scheme 23 Asymmetric aza-Claisen rearrangement and von Braun dealkylation pathway

The levels of diastereoselectivity obtained from the rearrangements were generally excellent. The stereochemical course of the reaction has been described using the chair- and boat-like intermediates given in Scheme 24. Similarly to Belluš (see previous section), Nubbemeyer *et al*. explained their results by assuming that chair transition states are adopted and that allylic strain is minimised, hence giving four reactive chair conformations that the reaction could go through (**158**, **160**, **161** and **162**). Of these conformations, **158** and **160** are expected to be most favourable since attack from the vinyl double bond onto the allylic double bond would take place from the less hindered side; conformation **160** is lower in energy than **158** as it lacks steric clashes between the hydrogen atom or R-group and 5-membered ring.



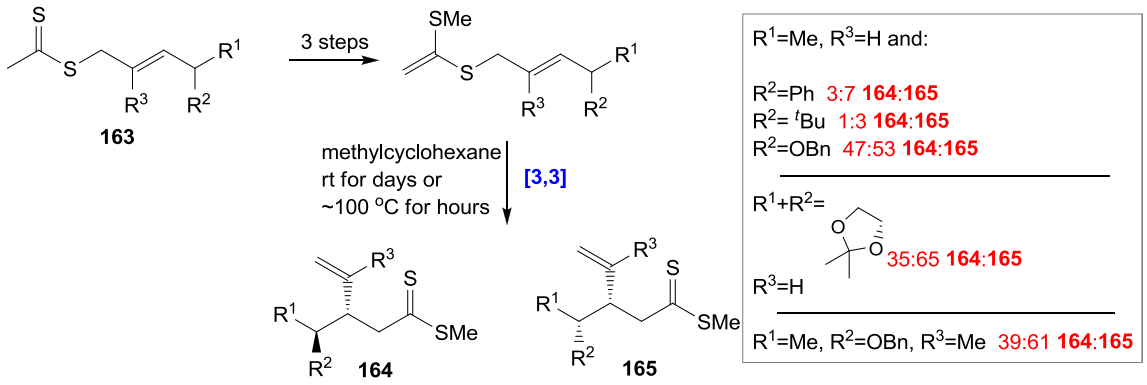
Scheme 24 Hypothetical transition states

When R=H (hence **158**=**160** and **161**=**162**), a low ratio of 3:2 **155**:**156** was obtained. As expected, increasing the bulkiness of the R-group from a hydrogen atom to a larger group (e.g. ^{i}Pr or CH_2=CH_2) raised the ratio of the expected major conformations **154**:**155** to 1:97, along with trace amounts of **156** and **157**. Interestingly, when the R-group had an extended π-system (e.g. Ph or CH=CHCH=CH), product **154** was predominant. This is presumably because either the reaction proceeds via boat-like conformation **159** (although there is no obvious reason why this would happen for these substrates), or that some electronic aspect of the extended conjugation into the phenyl and butadiene systems results in conformation **158** being adopted.

1.5.3.1.3 Thia-Claisen rearrangements

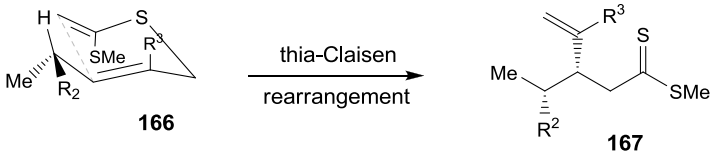
Metzner and co-workers have performed some moderately diastereoselective thia-Claisen rearrangements.[58] The precursors to these [3,3]-rearrangements were synthesised in 3 steps from allyl dithioester **163**; thia-Claisen rearrangements were then carried out in methylcyclohexane at room temperature or reflux (Scheme 25). Initially,

[3,3]-rearrangements with a substrate that had the substituents R^1 and R^3 fixed as methyl and H respectively while R^2 was varied, were attempted. The levels of diastereoselectivity obtained were generally quite low, however, with R^2=^{t}Bu, a 1:3 ratio of **164**:**165** was achieved.



Scheme 25 Thia-Claisen rearrangements

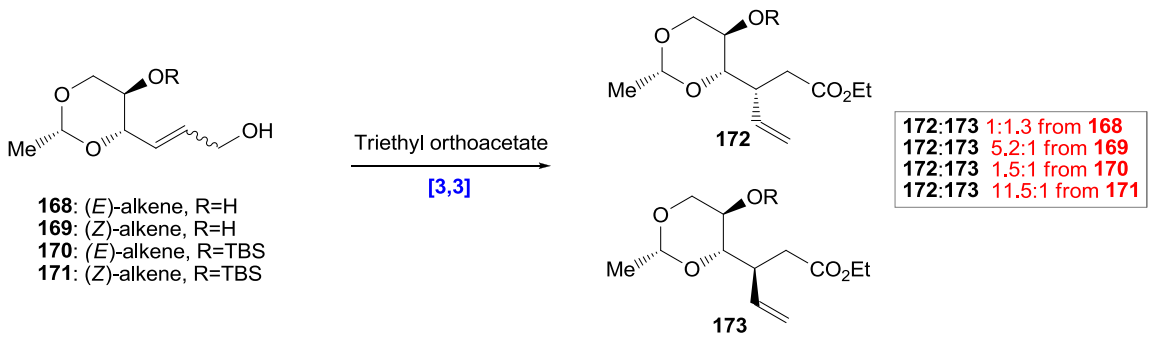
Metzner believes that conformation **166** is the most likely, since it has the smallest group (the hydrogen atom) in the inside position, the medium sized group (Me) in the *outside* position and the alkoxy group (R^2) perpendicular to C=C so that attack from the vinyl double bond takes place antiperiplanar to it (Scheme 26).



Scheme 26 Reactive pathway for thia-Claisen rearrangements

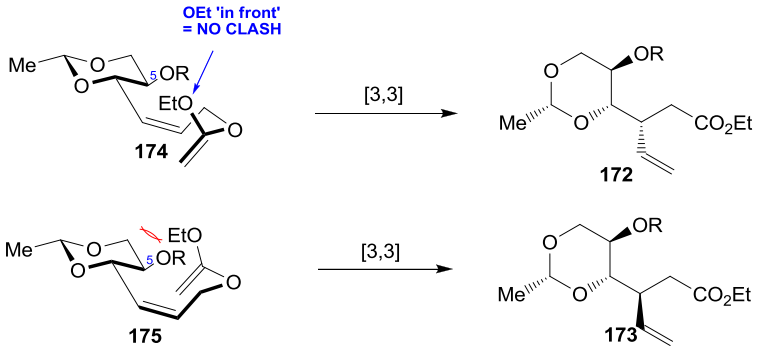
1.5.3.1.4 Johnson-Claisen rearrangements

Ogawa *et al*. have investigated the effect that substituted dioxane units have on Johnson-Claisen rearrangements (Scheme 27).[59] Upon [3,3]-sigmatropic rearrangement of compound **168**, diastereomers **172** and **173** were obtained in a 1:1.3 **172**:**173** ratio; however, (*Z*)-analogue **169** gave a 5.2:1 ratio of **172**:**173**. Replacement of the hydroxyl group in **168** and **169** with the bulky TBS group to give **170** and **171** respectively was effective in increasing the diastereoselectivity from 1:1.3 to 1.5:1 for **170** and 5:1 to 11.5:1 for **171**.



Scheme 27 Asymmetric Johnson-Claisen rearrangements

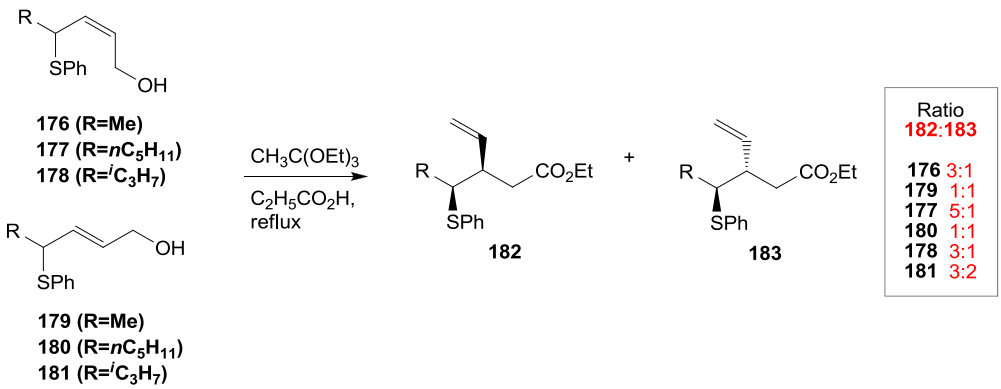
Ogawa has accounted for the preferential formation of product **172** over **173** in the reactions involving (*Z*)-alcohols **169** and **171** using reactive conformations **174** and **175**, which both possess minimal allylic strain (Scheme 28). Conformation **175** suffers from a steric clash between the C^5 substituent and the OR substituent of the dioxane ring and hence attack onto the allylic portion would be from the *more* hindered face. However, conformation **174** has no such problem and is therefore more favourable, since attack onto the allyl group is from the least hinderd side. Unsurprisingly, increasing the bulk of the R-group increases this effect and hence results in a larger ratio.



Scheme 28 Reactive conformation for ortho Johnson-Claisen rearrangement

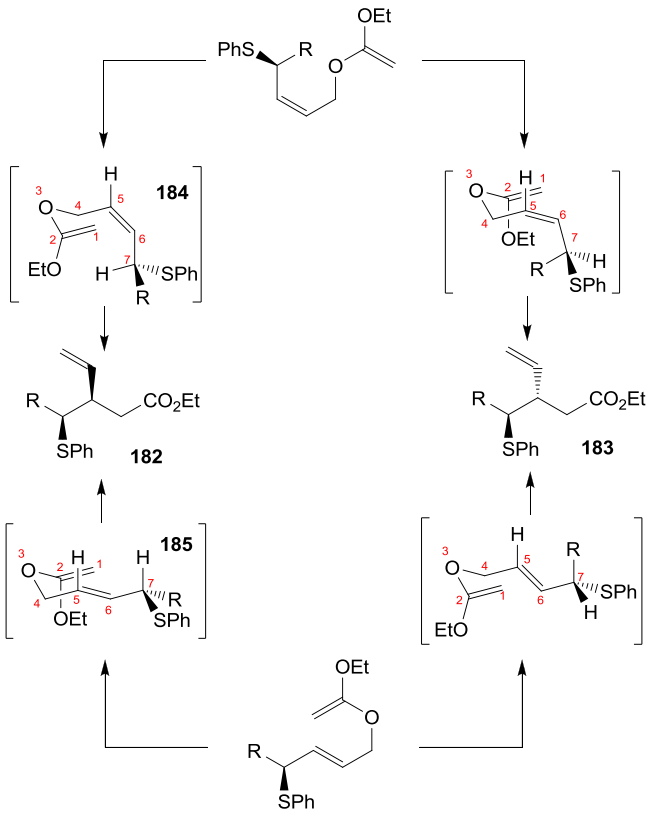
For (*E*)-alcohols **168** and **170**, there is no such clash in either conformation and hence the difference in energy between the two possible conformations is small, leading to a low diastereomeric ratio.

More recently, Craig *et al*. studied the Johnson-Claisen rearrangements of of (*E*)- and (*Z*)-allylic alcohols bearing a sulfur substituent and have also shown that variation of the allylic substitution pattern can lead to changes in the diastereoselectivity.[60] It was found that (*E*)-alkene **179** (where R=Me) underwent a completely unselective rearrangement. However, (*Z*)-alkene **176** gave a 3:1 mixture of products in good yield; other R-groups resulted in similar trends (Scheme 29)



Scheme 29 Johnson-Claisen rearrangement reactions

Craig *et al*. explained these findings by assuming that with the (*Z*)-double bond geometry, the major product arises from conformation **184**, whereby the C^7-H bond, rather than the C^7-R bond, eclipses the allylic C^4-C^5 bond to mimise allylic strain; attack from the vinyl moiety onto the allylic portion is then from the opposite face to the C-S bond. However, for the (*E*)-double bond geometry, the lesser steric bulk associated with the C^5-H bond compared to the C^4-C^5 bond (as in conformation **185**) leads to lower selectivity (Scheme 30).



Scheme 30 Rationale for stereochemical outcome of Johnson-Claisen rearrangement

In other work on Johnson-Claisen rearrangements, Suzuki *et al*. have shown substrates such as **187** to undergo [3,3]-sigmatropic rearrangement with selectivity of around 3:1 for both the (*E*)- and (*Z*)- alkene precursor (Figure 12).[61] Similarly, Takano *et al*. found that precursor **186**, which is analogous to **187** except for the additional methyl group on the double bond, gave no preference for either diastereoisomer of product (Figure 12).[62]

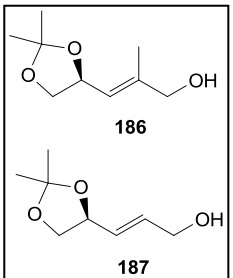
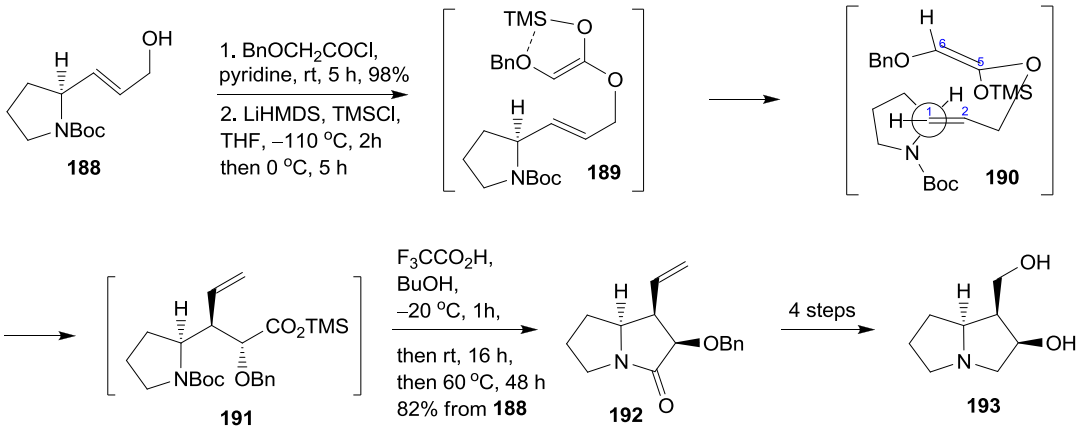


Figure 12

1.5.3.1.5 Ireland-Claisen rearrangements

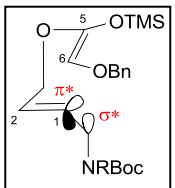
Mulzer *et al*. employed a highly diastereoselective Ireland-Claisen rearrangement whilst working towards the synthesis of (−)-petasinecine (Scheme 31).[63] The precursor **189** for the key rearrangement was formed by reaction of allyl alcohol **188** with an acid chloride in the presence of pyridine; treatment of this ester with LiHMDS and trimethylsilyl chloride at low temperature promoted the [3,3]-sigmatropic rearrangement to form product **191** via **190**. Rearranged product **191** was not isolated but converted *in situ* into bicycle **192**, which itself was isolated as a single diastereoisomer. A four step linear sequence then converted **192** into desired alkaloid **193**.



Scheme 31 Mulzer's diastereoselective Ireland-Claisen rearrangement en route towards (−)-petasinecine

Mulzer and co-workers attributed this faultless diastereoselective reaction to the following two points: (i) deprotonation using LiHMDS occurs to give stereospecifically the (*Z*)-enolate due to chelation; (ii) a chair conformation is adopted. With these two conditions in place, Mulzer chose to explain the diastereoselectivity using reactive

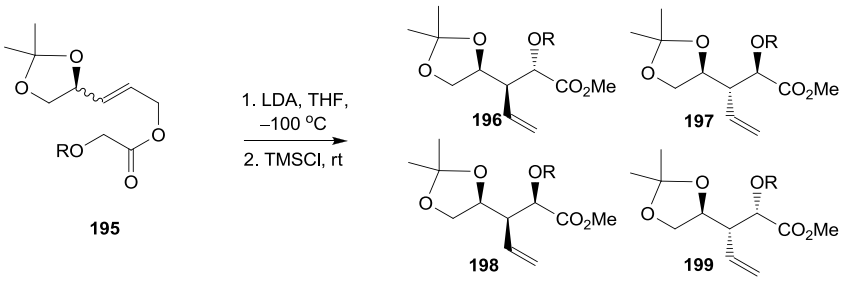
conformation **190**, in which attack from the vinyl moiety occurs *anti* to the C-N bond, giving diastereoisomer **191** as the sole product.



194, Figure 13

Another factor contributing to the high level of diastereoselectivity obtained is the low temperature at which the rearrangement step is performed. It is believed that the strong electron withdrawing nature of the Boc group helps to lower the energy of the 1,2-π* orbital via a σ*-π* interaction (**194**, 194, Figure 13). In addition, the electron donating ability of the OBn and OTMS group on the vinyl fragment increases the energy of the 5,6-π-orbital; a combination of these two effects leads to a strong HOMO-LUMO interaction and hence the reaction can be conducted at low temperatures.

Cha *et al*. have also performed diastereoselective chelation-controlled Ireland-Claisen rearrangements; however their approach employs the acetonide unit to provide the extra-annular stereogenic centre (Scheme 32).[64] This strategy provided moderate to good diastereomeric ratios upon [3,3]-sigmatropic rearrangement. This work should be compared to that described by Mulzer *et al*. in the previous section; the noticeable differences between the two studies are that Cha's work incorporates the stereogenic centre into an acetonide unit instead of a pyrrolidine, and that the rearrangement is carried out at room temperature, not 0 °C.

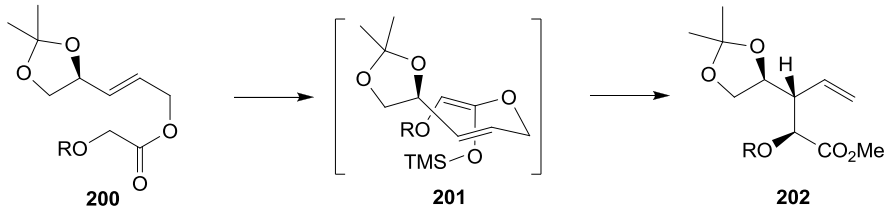


Ratio 196:197:198:199		
R=H:	(*Z*)	**1** : **1.4**
	(*E*)	: **1** : **1.3**
R=Me:	(*Z*)	0.5 : 0.3 : **9** : **1**
	(*E*)	**4.4** : **1** : 0.2 : 0.3
R=MOM	(*Z*)	0.1 : 0.2 : **1** : **0.2**
	(*E*)	**4** : **1** : 0.3 : 0.2
R=Bn	(*Z*)	0.3 : 0.3 : **5** : **1**
	(*E*)	**4.2** : **1** : 0.3 : 0.1

Scheme 32 Cha's diastereoselective Ireland-Claisen rearrangements

Cha's results indicate that when R=H, low diastereomeric ratios are obtained from the rearrangements; however, increasing the size of the R-group provides much improved

diastereomeric ratios. When R=Bn, the level of diastereoselectivity achieved is still not as high as that obtained by Mulzer on a similar substrate (Scheme 31); one reason for the difference in diastereoselectivity obtained could be that Mulzer's rearrangement was carried out at a lower temperature (this was made possible due to the electron withdrawing nature of the NBoc group).

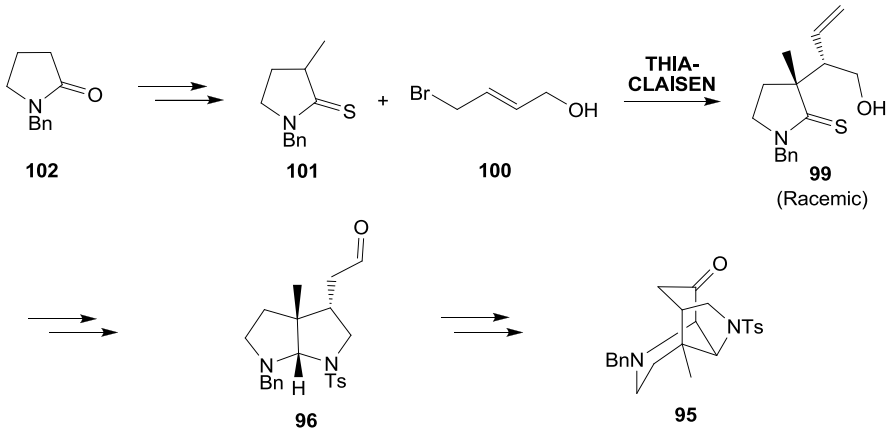


Scheme 33 Reactive conformation for Ireland-Claisen rearrangement with (*E*)-double bond

The major products **202** from these rearrangements are believed to arise from reactive conformation **201** (Scheme 33 – shown is reactive conformation for the (*E*)-alkene precursor). This conformation is chair-like, contains a (*Z*)-silyl enol ether and is positioned so that an attack from the vinyl double bond onto the allylic portion is *anti* with respect to the alkoxy group.

2 Asymmetric thia-Claisen rearrangements[65,66,67]

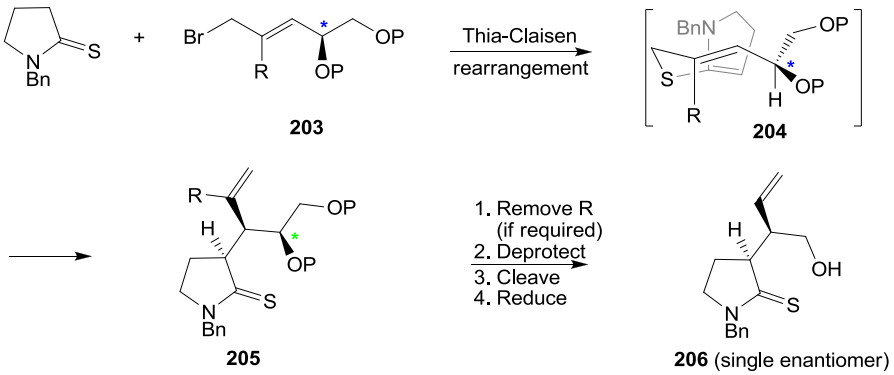
In the Porter group's current synthetic approach towards the sarain core (Scheme 34), a thia-Claisen rearrangement is employed as one of the key steps.[28] However, although this rearrangement is efficient in providing the correct relative stereochemistry of thiolactam **99**, the product is racemic. As a result, we sought an asymmetric variant of this rearrangement.



Scheme 34 Thia-Claisen rearrangement as a key step towards sarain core **95**

2.1 Strategy

We envisaged that use of a chiral bromide with general structure **203** may result in preferential formation of one diastereomeric product. In accord with the literature shown in section 1.5.3, the reaction would proceed via chair conformation **204**, in which attack onto the double bond would take place from the opposite side to the allylic oxygen and minimal $A^{1,3}$-strain would be present (Scheme 35).



Scheme 35 Proposed asymmetric thia-Claisen rearrangement

In addition, the effect of placing a *removable* bulky group onto the double bond of the bromide was to be tested. We expected this to increase $A^{1,3}$-strain, thus making conformation **204** even more favourable. If this rearrangement was successful, the protecting groups could be removed, the diol cleaved and resultant aldehyde reduced to give target molecule **206** as a single enantiomer.

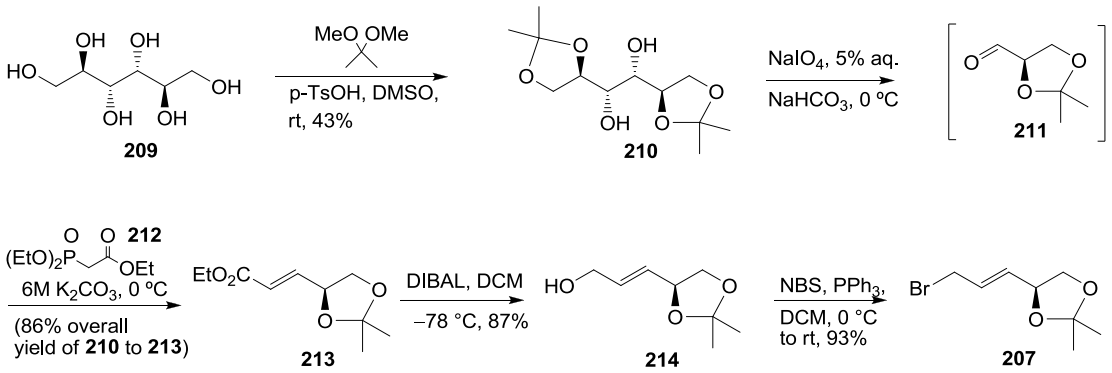
Initially bromides **207** and **208** were targeted (Figure 14); it was anticipated that these could both be prepared from D-mannitol **209** (Scheme 36).[68,69] The following two sections will describe our syntheses of these compounds.

207 **208**

Figure 14 Bromide targets **207** and **208**

2.2 Formation of acetonide protected precursor

D-Mannitol **209** was selectively protected at its 1,2- and 5,6-diol units to afford diol **210** in 43% yield. The method employed was an acid catalysed transacetalisation; the relatively low yield obtained is thought to be a consequence of the protection not being totally selective (Scheme 36).



Scheme 36 Syntheic route towards bromide precursor

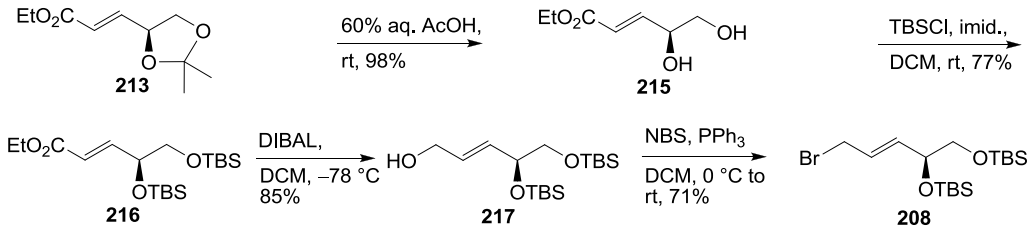
Conversion of diol **210** to α,β-unsaturated ester **213** was achieved by an oxidative cleavage and olefination; the aldehyde resulting from oxidative cleavage of **210** is known to be sensitive to racemisation and hence preferentially should not be isolated in order to preserve the stereochemistry at the chiral centre. A number of protocols have

been developed to avoid isolation of this compound and in this case, the procedure of Marshall *et al.* was chosen and implemented.[68,69]

Thus, treatment of **210** with sodium periodate in aqueous sodium bicarbonate, followed by addition of triethyl phosphonoacetate **212** and K_2CO_3 afforded α,β-unsaturated ester **213** in 96% yield, with a selectivity of *ca.* 25:1 *E*:Z.[68] DIBAL reduction of ester **213** proceeded smoothly to afford (*E*)-allylic alcohol **214** in 77% yield; alcohol **214** was then converted to bromide **207** using *N*-bromosuccinimide and triphenylphosphine in 93% yield.[70]

2.3 Formation of bis-silyl ether protected precursor

Formation of bis-silyl ether **208** was achieved in four steps from ester **213** (Scheme 37). The synthesis involved treatment of **213** with 60% aqueous acetic acid at room temperature to form diol **215**, followed by TBS protection using a standard procedure to give ester **216**.



Scheme 37 Four step conversion of ester **213** into bromide **208**

As with the synthesis of bromide **207** (section 2.2), DIBAL reduction of ester **216**, followed by bromination using *N*-bromosuccinimide and triphenylphosphine, gave bis-silyl ether **208** in good yield.

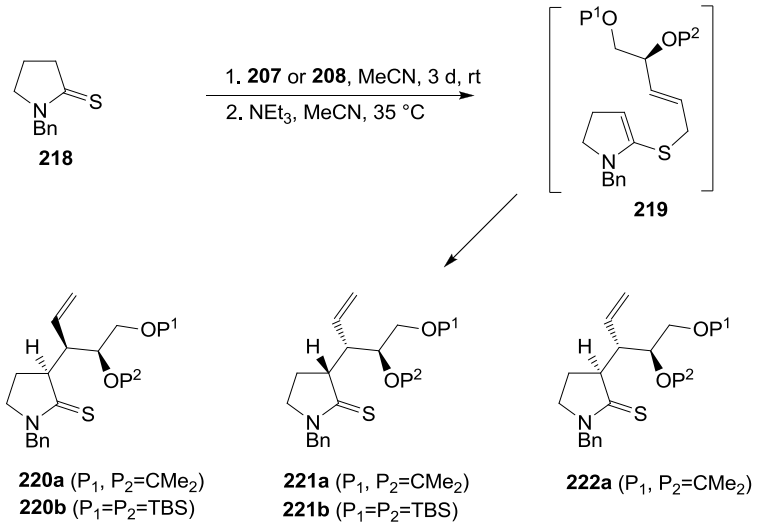
2.4 Thia-Claisen rearrangement

N-Benzylpyrrolidine-2-thione (**218**) was prepared from lactam **102** (Figure 15) using Lawesson's reagent in THF, in 72% yield.[71] *S*-alkylation of thioamide **218** with bromides **207** and **208** in acetonitrile in the presence of 4 Å molecular sieves was followed by deprotonation

102

Figure 15

of the salts with triethylamine at 35 °C.[28] Gratifyingly, the thia-Claisen rearrangement occurred to afford a mixture of thiolactam products (Scheme 38); the results are summarised in Table 1.



Scheme 38 Thia-Claisen rearrangements

Entry	Bromide	Ratio[a]	Yield of **220** / %[b]	Yield of **221** / %[b]	Yield of **222** / %[b]
1	**207**	2.5:1:0.1 **220a**:**221a**:**222a**	38	10	1
2	**208**	30:1 **220b**:**221b**	41	1	Not isolated

[a] Ratios measured from the ^{1}H NMR spectrum of the crude reaction mixture. [b] Isolated yields of individual stereoisomers

Table 1 Product ratios from thia-Claisen rearrangements

As expected, the major products were diastereoisomers **220a/b** and **221a/b**, arising from a chair transition state, with only a trace amount of a third diastereoisomer **222a** isolated from the acetonide-protected substrate **207** (entry 1). Although the stereochemical assignments of lactams **220-222** were not known at this stage, we were later able to confirm their structures through a combination of X-ray crystallography and chemical correlations (section 2.7).

The thia-Claisen rearrangements occurred successfully; however, the level of diastereoselectivity obtained was disappointingly low for the rearrangement involving acetonide **207** (*ca.* 2.5:1), reflecting a low level of facial selectivity imparted upon the exocyclic double bond by the adjacent stereocentre in intermediate **219**. However, an

excellent diastereomeric ratio was obtained for the [3,3]-sigmatropic rearrangement involving TBS protected bromide **208** (*ca*. 30:1), albeit in relatively low yield.

2.5 Modification of precursors: bromination

To overcome the issue of low diastereoselectivity that was obtained for the acetonide series (bromide **207**), and bias the conformation of intermediate **219** towards a single rotamer, a vinylic substituent was introduced into the bromide precursor; it was believed that this could improve the diastereoselectivity because of increased allylic strain in the transition state. Therefore, we decided to introduce a bromine substituent (which could be removed at a later stage) onto the double bond of the rearrangement substrate. We also decided to do the same thing on TBS protected bromide **208**, to see if any improvement on the excellent chiral induction already obtained could be achieved, and overcome the poor yield. Our synthesis was thus modified to produce bromides **223** and **224** (Figure 16), which contain a bromine substituent on the double bond.

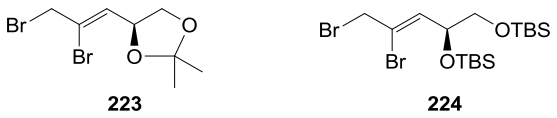
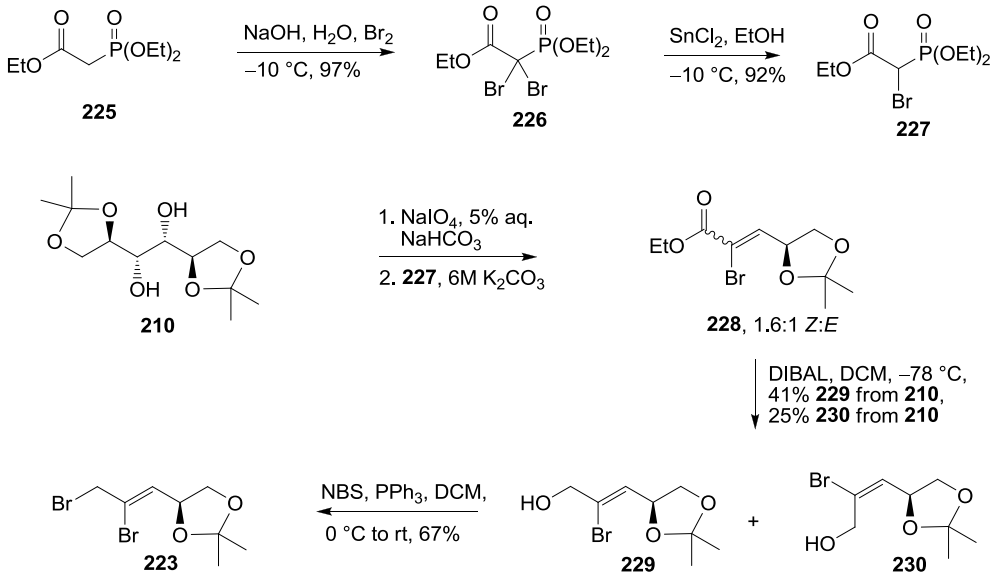


Figure 16 Dibromide targets

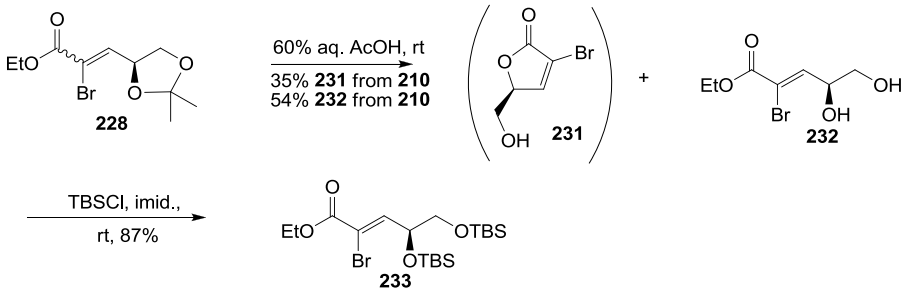
Brominated phosphonate reagent **227** was prepared from phosphonate **225** in two steps.[72] Firstly, treatment with aqueous sodium hydroxide and bromine solution formed dibromide **226** in 97% yield (Scheme 39). This reaction was capricious, and it was found that a reproducible yield could only be obtained if the internal reaction temperature was kept below 10 °C at all times throughout the addition of phosphonate **225** and the product was extracted into chloroform immediately after the reaction. Subsequently, monodehalogenation of **226** using tin(II) chloride afforded **227** in 92% yield. Care had to be taken during this reaction to avoid removal of the second bromine atom from **226**. Hence, cautious addition of the tin(II) chloride solution and regular analysis of the reaction mixture by TLC was essential.



Scheme 39 Formation of brominated phosphonate **227**, and synthetic route toward bromide **223**

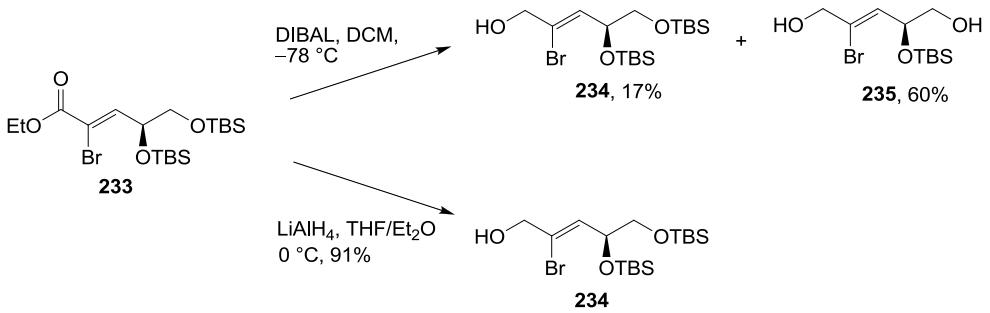
Diol **210** was treated with sodium periodate, and the resulting aldehyde reacted with brominated phosphonate **227** under analogous conditions to those used previously (section 2.2) giving an inseparable mixture of esters **228** in a 1.6:1 *Z:E* ratio. Following this olefination, the mixture of esters was reduced using DIBAL to give allylic alcohols **229** and **230**, which were separable by column chromatography and were obtained in 41% and 25% yield respectively from **210**. The major (*Z*)-alcohol **229** was treated with *N*-bromosuccinimide and triphenylphosphine to give the desired bromide **223** in 67% yield (Scheme 39).

To synthesise bromide **224**, ester mixture **228** was deprotected using 60% aqueous acetic acid to afford the expected (*Z*)- diol **232**. The (*E*)- diol reacted further and 5-membered lactone **231** was obtained (Scheme 40).



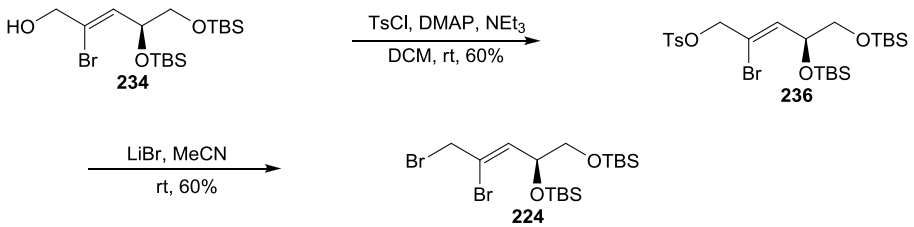
Scheme 40 Deprotection of ester **228** and subsequent TBS protection of (*Z*)-diol **232**

TBS protection of (*Z*)-diol **232** was next accomplished using TBS chloride and imidazole in 87% yield to give ester **233** (Scheme 40). Reduction of ester **233** was first attempted using DIBAL as before; however the major product was not the expected bis-silyl ether (which was isolated in 17% yield), but mono-silyl ether **235** (Scheme 41). Although we cannot be certain as to which TBS group had been removed during the reduction, it is more likely that the primary one had been excised, as primary silyl ethers are typically more labile than secondary ones.



Scheme 41 DIBAL and $LiAlH_4$ reductions of ester **233**

Changing the reducing agent to $LiAlH_4$ gave clean conversion of **233** to alcohol **234** in 91% yield, with no purification step required (Scheme 41). Initial attempts to convert alcohol **234** into bromide **224** using *N*-bromosuccinimide and triphenylphosphine were unsuccessful. The reaction gave a mixture of products, which not only made isolation of the desired bromide difficult, but also reduced the yield dramatically. Hence, as an alternative protocol, tosylation of alcohol **234** using tosyl chloride, triethylamine and DMAP gave tosylate **236** in 60% yield, followed by reaction with LiBr, which gave the desired bromide (**224**, Scheme 42) in 60% yield.[73]

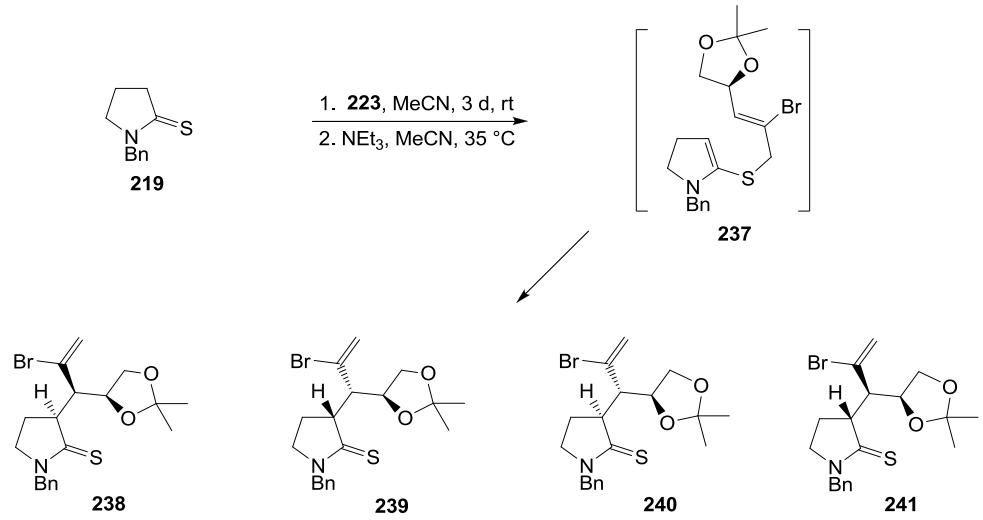


Scheme 42 Two step conversion of alcohol **234** into bromide **224**

2.6 Thia-Claisen rearrangement of bromo-alkene substrates

Bromide **223** was next employed in the thia-Claisen rearrangement. When subjected to the same conditions as used previously, thiolactams **238**, **239** and **240** were obtained in

2%, 52% and 2% yields respectively, with excellent diastereoselectivity (Scheme 43); the results are summarised in Table 2.



Scheme 43 Thia-Claisen Rearrangements

Bromide	Ratio[a] **238**:**239**:**240**:**241**	Yield of **238** / %	Yield of **239** / %	Yield of **240** / %	Yield of **241** / %
223	1:12.2:0.6:*ca*. 0.1	2	52	2	Not isolated

[a] Ratios measured from the ^{1}H NMR spectrum of the crude reaction mixture

Table 2 Product ratios from thia-Claisen rearrangement

Although the fourth isomer **241** was not isolated from this reaction, it was isolated when the rearrangement was carried out using the (*E*)-analogue of bromide **223** (section 2.5). As a result, the characteristic signals of lactam **241** were known and therefore it could be identified in the crude ^{1}H NMR spectrum, enabling a diastereomeric ratio for the product to be deduced for this rearrangement.

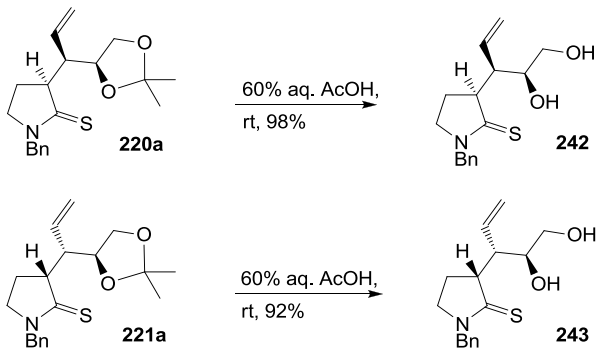
Interestingly, the major product from this rearrangement was the (2*R*, 3'*S*, 4'*S*)-isomer **239**, in contrast to the non-brominated substrate which gave primarily the (2*S*, 3'*R*, 4'*S*)-isomer **220** (which has the same stereochemistry as **238**). Similarly to the non-brominated lactams **220**-**222**, assignment of products **238**-**241** was not possible at this stage; however, these were determined after further studies (section 2.7).

We next attempted the rearrangement with bromide **224**; disappointingly, for reasons unknown, the desired thia-Claisen rearrangement did not occur on any occasion despite several attempts.

2.7 Assignment of the configuration of thia-Claisen products*

2.7.1 Non-brominated series

It was hoped that the stereochemistry of thiolactams **220**-**221** could be deduced in the most direct manner, i.e. using X-ray crystallography. Unfortunately this was not possible as the rearrangement products were not crystalline. However, after deprotecting thiolactams **220a** and **221a** using 60% aqueous acetic acid at room temperature, two diastereomeric diols were generated (**242** and **243** respectively) in excellent yield, with **243** being sufficiently crystalline to obtain a high-quality single crystal (Scheme 44). Its structure was unambiguously assigned by X-ray crystallography and thus, this revealed the stereochemistry of **221a** (Figure 17).



Scheme 44 Deprotection of lactams **220a** and **221a**

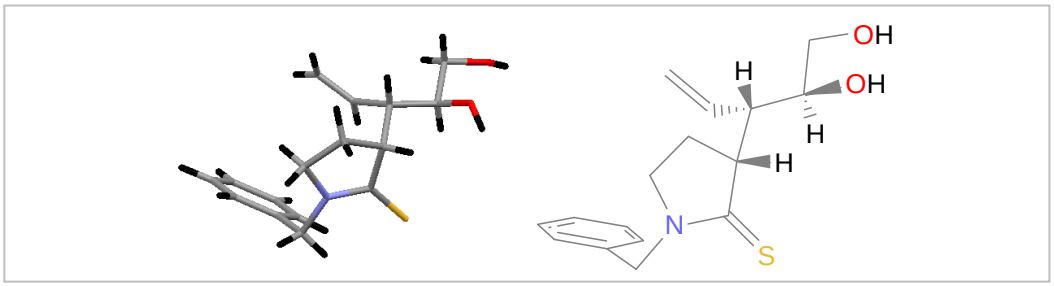
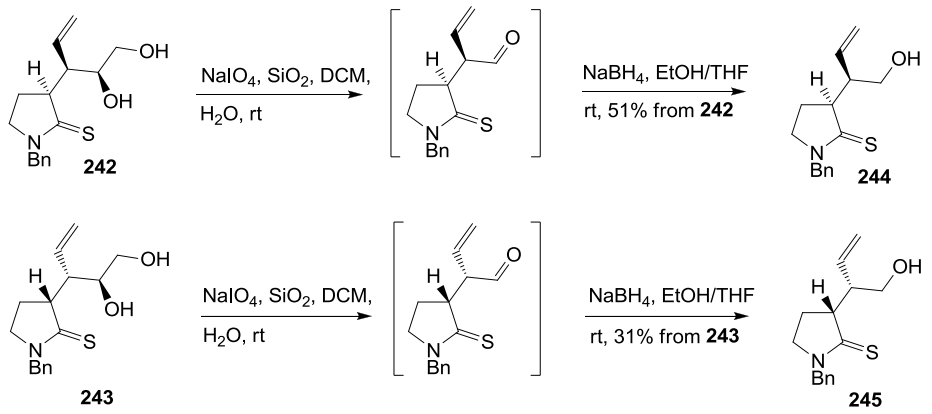


Figure 17 X-ray crystal structure of diol **243**

Assignment of the stereochemistry of **220a** was achieved indirectly by cleavage of each of diols **242** and **243** using silica gel-supported sodium periodate (Scheme 45), and reduction of the intermediate aldehydes (which were not isolated) using sodium borohydride to give alcohols **244** and **245**, which was achieved in moderate yield.[74]

* When the thia-Claisen rearrangements were carried out, the stereochemistries of the products were not known; however, for clarity, all of the structures are depicted with the stereochemistry that was deduced from these studies.

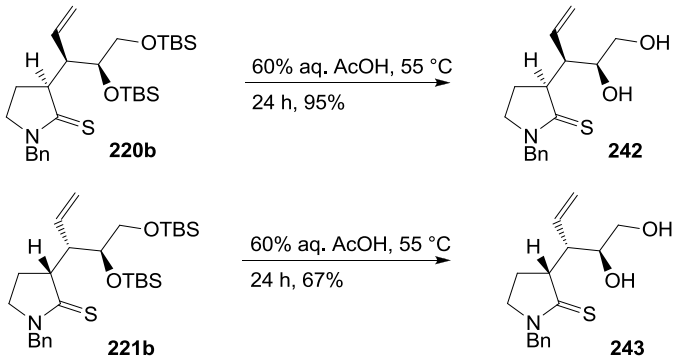
These products had identical ^{1}H NMR data, but opposite specific rotations ($[\alpha]_D^{20}$ = –73.2 and $[\alpha]_D^{20}$ = +71.4 respectively), and hence these alcohols **244** and **245** could be identified as enantiomeric. Therefore, the stereochemistry of **220a** could be assigned, as having the opposite configuration at the 2 and 3' stereogenic centres to **221a**.



Scheme 45 Cleavage of diols **242** and **243**, followed by $NaBH_4$ reduction

The stereochemical assignment of thiolactam **222** was not possible at this point, however, this assignment was successfully made later (section 2.7).

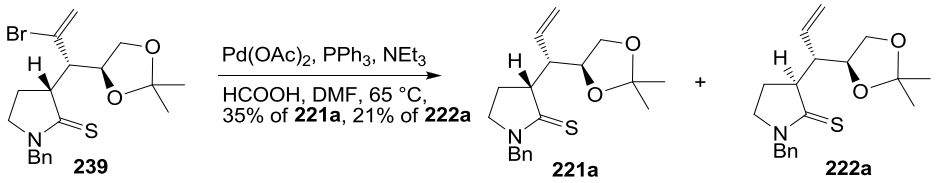
Previous attempts within the Porter group to undertake silyl deprotection of thiolactams similar to **220b** and **221b** using TBAF resulted in epimerisation at the position α- to the thiocarbonyl.[28] With this in mind, we sought a different method for the deprotection. Gratifyingly, deprotection of **220b** and **221b** using 60% aqueous acetic acid at 55 °C overnight afforded two diols, which were identified as thiolactams **242** and **243** in 95% and 67% yield respectively (Scheme 46). Hence, this revealed the stereochemistry of rearrangement products **220b** and **221b**.



Scheme 46 Deprotection of thiolactams **220b** and **221b**

2.7.2 Brominated series

In order to correlate the brominated series to the non-brominated series, the bromine substituent on the double bond of thiolactams **238-241** had to be removed. Initial attempts at removal of the bromine substituent involved treatment of thiolactam **239** with palladium acetate, formic acid, triphenylphosphine and triethylamine.[75] The optimised conditions were found to require 30 equivalents of triethylamine and 20 equivalents of formic acid for complete conversion of starting material. Debromination gave a mixture of two products **221a** and **222a** (Scheme 47), whose structures were confirmed by ^{1}H NMR comparison with the rearrangement products from the non-brominated series.

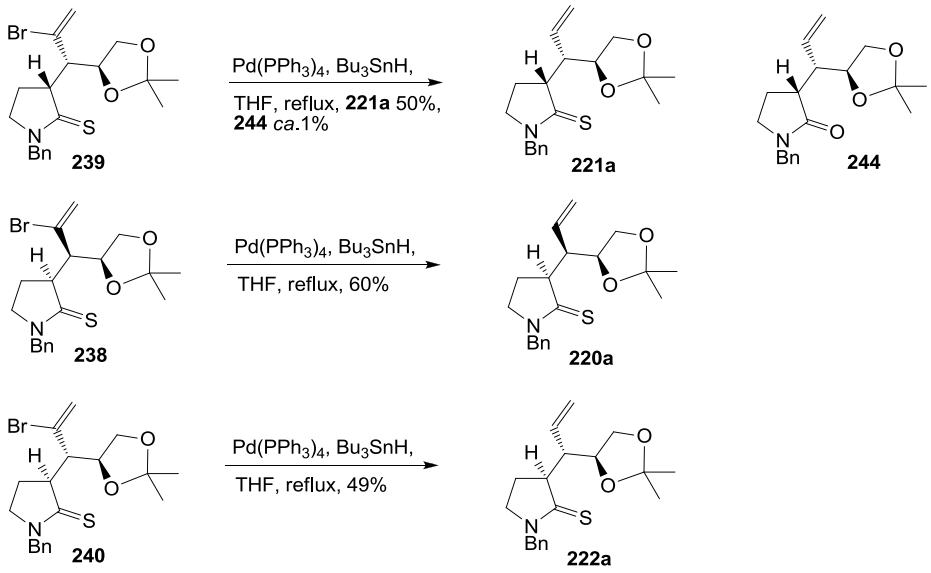


Scheme 47 Palladium catalysed debromination of **239** using HCOOH

The presence of two stereoisomers suggested that epimerisation α-to the thiocarbonyl group had taken place. Hence, whilst this result did not allow definite assignment of the stereochemistry of brominated thiolactam **239**, it did indicate that the previously assigned diastereoisomer **221a** was epimeric with **222a** at the position α- to the thicarbonyl group (*vide supra*). As the stereochemistry of diastereomer **221a** had already been unambiguously assigned, the configuration of **222a** could be ascertained as that depicted.

We next carried out the palladium-catalysed debromination using tributyltin hydride as the reducing agent.[76] These conditions were chosen as they are neutral, which seemed appropriate as a base was thought to be the most likely cause of the epimerisation observed during the reaction involving triethylammonium formate.

Treatment of lactam **239** with $Pd(PPh_3)_4$ and tributyltin hydride afforded debrominated isomer **221a** in 50% yield, along with a small amount of lactam **244** (Scheme 48). As the stereochemistry of **221a** had previously been assigned, this result confirmed the stereochemistry of **239**.



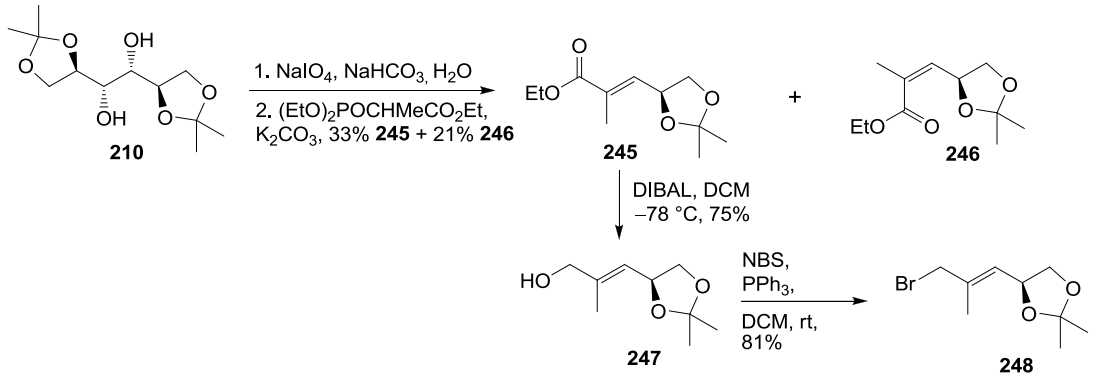
Scheme 48 Palladium catalysed debromination of lactams **238**-**240** using Bu_3SnH

Debromination using tributyltin hydride was also carried out for thiolactam **238**, giving thiolactam **220a** as the sole product in 60% yield, thus confirming the stereochemistry of thiolactam **238** (Scheme 48). For completeness, thiolactam **240** was debrominated under the same conditions to give, as expected, debrominated product **222a** in 49% yield.

2.8 Methylated bromide – effect on the thia-Claisen rearrangement

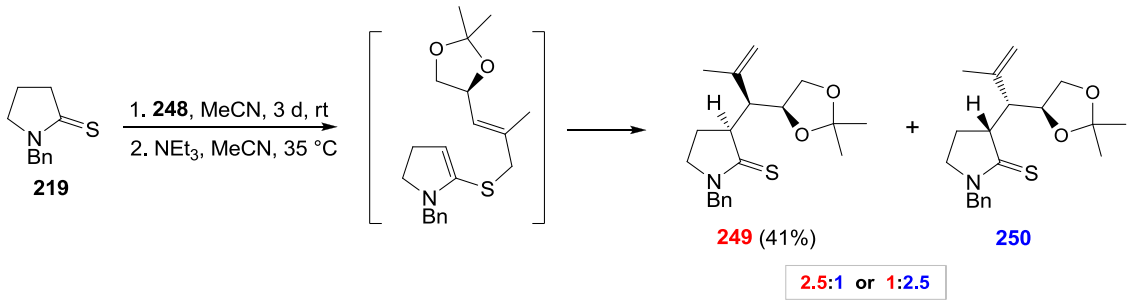
To help improve our understanding of the reactive conformations involved in the thia-Claisen rearrangements previously described, bromide **146** (which bears a methyl group on the double bond instead of a bromine or hydrogen atom) was to be tested in the thia-Claisen rearrangement (Scheme 49). It was thought that this could indicate the effect that steric and electronic effects have on the diastereoselectivity in the thia-Claisen rearrangement.

Bromide **248** was made in 3 steps from diol **210**; the synthesis started with cleavage of diol **210** using sodium periodate, followed by Wadsworth-Emmons olefination of the resulting aldehyde to give ester **245** (and ester **246**) that bears a methyl group on the double bond. DIBAL reduction of ester **245** gave alcohol **247**; this was followed by conversion into the corresponding bromide **248** (Scheme 49).



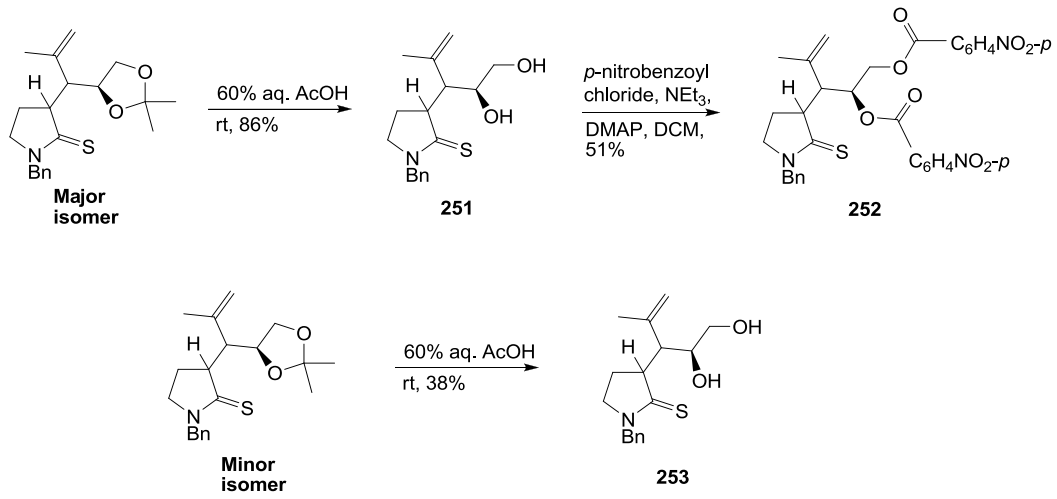
Scheme 49 Formation of methylated bromide precursor **248**

Bromide **248** was then subjected to the conditions previously described for thia-Claisen rearrangements; thiolactams **249** and **250** were isolated from the reaction in a ratio of 2.5:1 (Scheme 50). The minor diastereoisomer could only be obtained contaminated with a small amount of the major diastereoisomer. As a result, we tried to grow X-ray quality crystals of the major diastereoisomer only, in an attempt to reveal its absolute stereochemistry; however, this was not possible despite many attempts.



Scheme 50 Thia-Claisen rearrangement involving methylated bromide **248**

In order to determine the stereochemistry of the two newly formed centres in both **249** and **250** (and therefore reveal whether thiolactam **249** or **250** was the major product from the reaction), thiolactams **249** and **250** were converted to their corresponding diols by treatment with 60% aqueous acetic acid (**251** and **253** respectively, Scheme 51). However, although both diastereoisomers were obtained cleanly as determined by ^{1}H NMR analysis, we were again unable to grow X-ray crystals.



Scheme 51 Deprotection of thiolactam products

In a final attempt, diol **251** (which was derived from the major diasteroisomer) was converted into its di-*para*-nitrobenzoate **252**, with the hope that it would be more crystalline.[77] Disappointingly, once again we were again unable to grow X-ray quality crystals.

Having not been able to identify the stereochemistry at the two key stereocentres in thiolactams **249** and **250**, we cannot tell whether the added methyl group switches the diastereoselectivity from 2.5:1 **220a**:**221a** (Scheme 38, Table 1) to 1:2.5 **249**:**250** or whether it results in almost identical diastereoselectivity to the disubstituted alkene (i.e. 2.5:1 **249**:**250**).

2.9 Model for the stereoselectivity in thia-Claisen rearrangements

To rationalise the stereochemical course of these thia-Claisen rearrangements, the reactive conformations of intermediates **97** (Scheme 38, page 38) and **131** (Scheme 43, page 42) must be considered. To deduce such conformations, we must use consider the two explanations described in section 1.5.3.1 and assume that the thia-Claisen rearrangement takes place through a chair-like transition state.

2.9.1 Brominated *vs* non-brominated series

Three chair conformations can be used to explain the outcome of the rearrangements (**254**, **255** and **256**, Figure 19). Conformations **255** and **256** have the hydrogen atom eclipsed with the R-group to minimise allylic strain and hence, would be lowest in energy. However, conformation **256** would also have attack onto the allylic system from the double bond from the opposite side to the allylic oxygen. This, according to Houk's Rule, gives **256** some additional stabilisation over conformation **255**. The final conformation, **254**, leads to product **239**; this suffers from additional allylic strain (**254**).

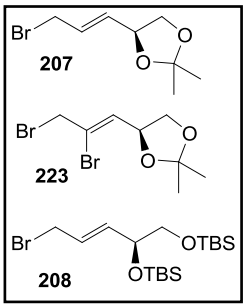


Figure 18

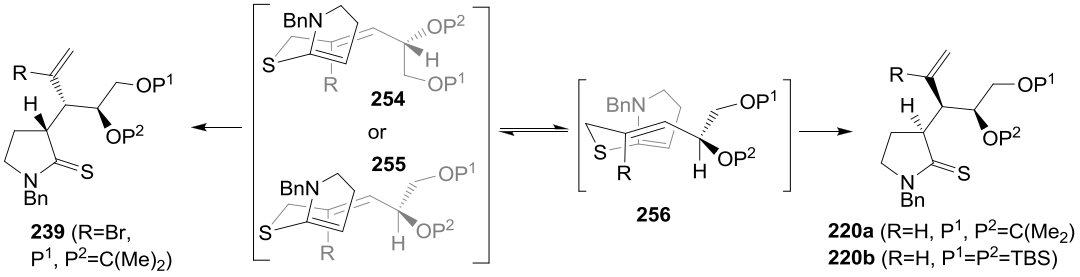


Figure 19 Possible reactive conformations for thia-Claisen rearrangements

This argument successfully predicts the reactions of **207** and **208**, but not **223**. In order to help explain the reversal of diastereoselectivity in going from bromides **207** to **223**, methylated bromide **248** (Figure 20) was made. We believed that the major product obtained from the thia-Claisen rearrangement involving this bromide would provide an indication on whether the steric or electronic effect of the additional bromine atom in bromide **223** was causing the reversal of diastereoselectivity. Unfortunately, the identity of the major diastereoisomer from the rearrangement involving methylated bromide **248** was not determined.

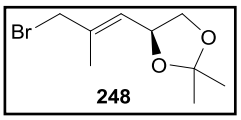


Figure 20

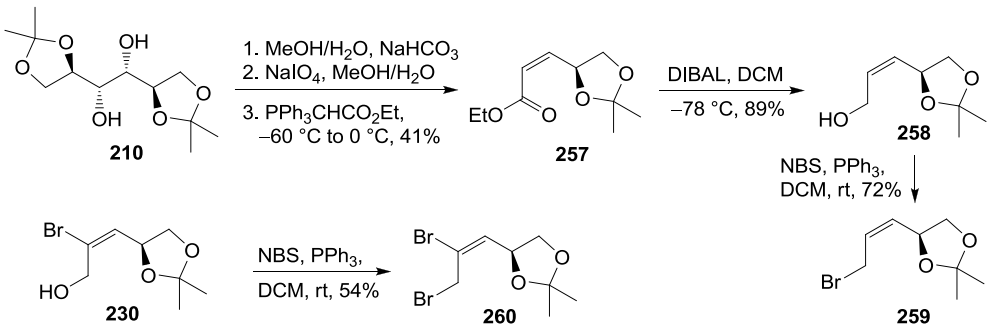
The reasons why dibromide **223** leads to **239** – presumably through conformation **255** – remain unclear. Hence, all that can be deduced is that electronic factors must be playing some role in increasing and inverting the sense of the diastereoselectivity between bromide **207** and dibromide **223**, as the highest level of diastereoselectivity obtained with either non-substituted **207** or methyl-substituted bromide **248** was only 2.5:1.

2.9.2 Acetonide *vs* TBS protecting group

The increased diastereoselectivity obtained in reactions with TBS protected bromide **208** (Figure 18) over its acetonide analogue **207** is most likely a consequence of the greater bulk of the TBS group, which increases the energy difference between conformation **256** and the alternative reactive conformations.

2.10 Thia-Claisen studies using *cis*-analogues

After the success achieved in the thia-Claisen rearrangements studied, we became interested in investigating the same [3,3]-sigmatropic rearrangements with the *cis*-analogues of **207** and **223** (**259** and **260** respectively), to see what level of asymmetric induction was achievable.[†] It was thought that these analogues could give better diastereoselectivity, as this has been the case for some rearrangements presented in the literature (section 1.5.3.1). Thus, bromide **259** was prepared in 3 steps from diacetonide **210**. The *cis*-olefin in ester **257** was formed via a low salt and low temperature Wittig reaction carried out under protic solvent conditions.[78,79] Alcohol **230**, synthesised previously, was converted to bromide **260** directly in 54% yield (Scheme 18).

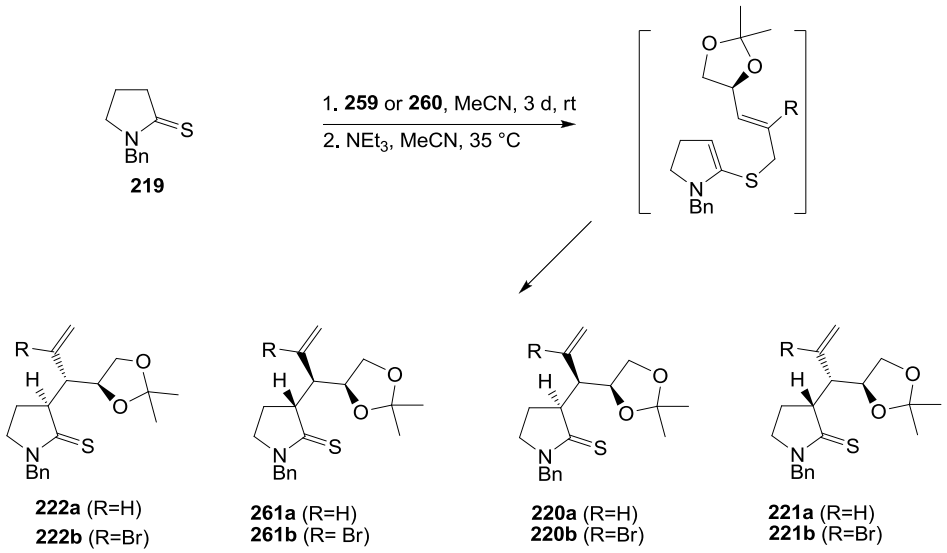


Scheme 52 Synthesis of *cis*-bromide analogues

The thia-Claisen rearrangement involving bromide **259** (Scheme 53) gave little asymmetric induction (*ca*. 2:0:1:1). Brominated substrate **260** on the other hand gave moderate diastereoselectivity (*ca*. 4:1:0:1); however, this was less than that achieved when using *trans*-bromide **223**. Interestingly, for the thia-Claisen rearrangement involving *cis*-bromide **259**, the fourth diastereomer **261** could not be identified in the ^{1}H

[†] There is a nomenclature switch between bromides **259** and **260**. Conventionally, these would be denoted (*Z*)-bromide and (*E*)-bromide respectively, since a bromine atom is of higher priority than a carbon atom. However, for simplicity, *cis* and *trans* have been used in this case to follow the carbon chain, not the priority atoms.

NMR spectrum of the crude material (it could not be isolated from the rearrangement involving *trans*-bromide **207** either), even though it was expected to be one of the two major products from this reaction. One possible explanation for this is that product **261** decomposes once formed; Table 3 summarises the results obtained.



Scheme 53 Thia-Claisen rearrangement

Entry	Bromide	Ratio[a]	Yield of **222** / %	Yield of **261** / %	Yield of **220** / %	Yield of **221** / %
1	**259**	2:1:1 **222a**:**220a**:**221a**	18	Not isolated	10	11
2	**260**	3.7:1:0.3:1 **222b**:**261b**:**220b**:**221b**	39	*ca.* 9	*ca.* 1	6

[a] Ratios measured from the ^{1}H NMR spectrum of the crude reaction mixture

Table 3 Product ratios from thia-Claisen rearrangement

2.10.1 Model for the stereoselectivity

According to the literature, the two most likely reactive conformations for these rearrangements should be those shown in Figure 21; allylic strain across the conjugated system is not affected by the nature of the R-group in these conformations. Both conformations have the same amount of allylic strain, however, since conformation **262** would involve attack from the double bond onto the opposite face of the allylic system to the C-O bond, we would expect this to be lower in energy than **263** due to the stabilisation discussed in section 1.5.3.1. However, this was not the case; in fact, **222a** and **222b** were the major products from the thia-Claisen rearrangement.

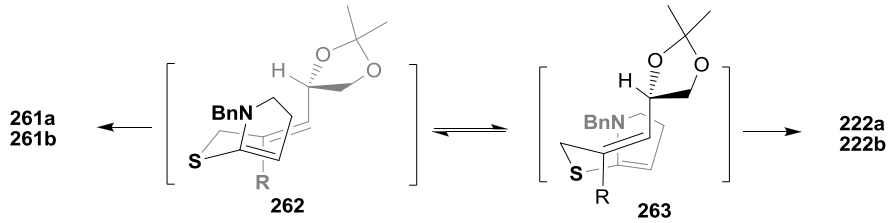


Figure 21 Expected, but not observed, reactive conformations for thia-Claisen rearrangements

This model is clearly not correct, and hence there must be an alternative explanation. However, there is no obvious reason why the above conformations would not be adopted, and why **262** would not be of lower energy than **263**. As a result, we are keen to perform computational work in the near future to help identify the reactive conformations adopted during this reaction.

3 Approaches towards the sarain core

Two new approaches towards the sarain core have been investigated and these will be discussed in the following section. The first approach investigates the use of halocarbenes to form ammonium ylids, while the second method is an altered version of the route described in section 1.4.7.

3.1 Ring expansion approach to the core

Although previous strategies adopted by the Porter group towards the core of sarain A involved the extension of the aldehyde side-chain of **96** prior to insertion into a C-N bond (Figure 22, top),[28] an alternative strategy would be to perform the C-N insertion prior to C-C bond formation (Figure 22, bottom).

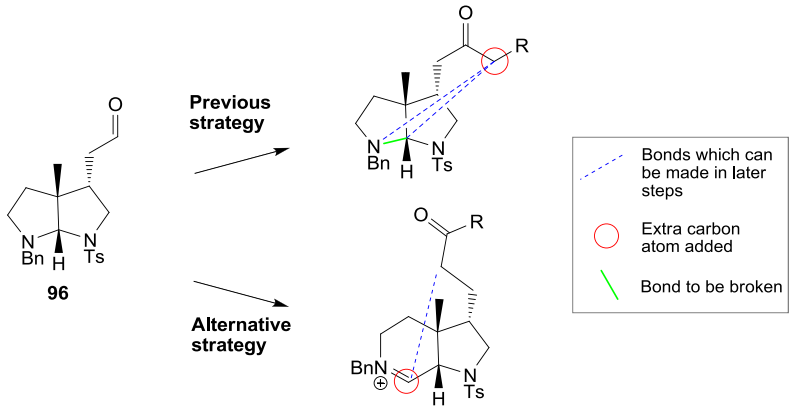
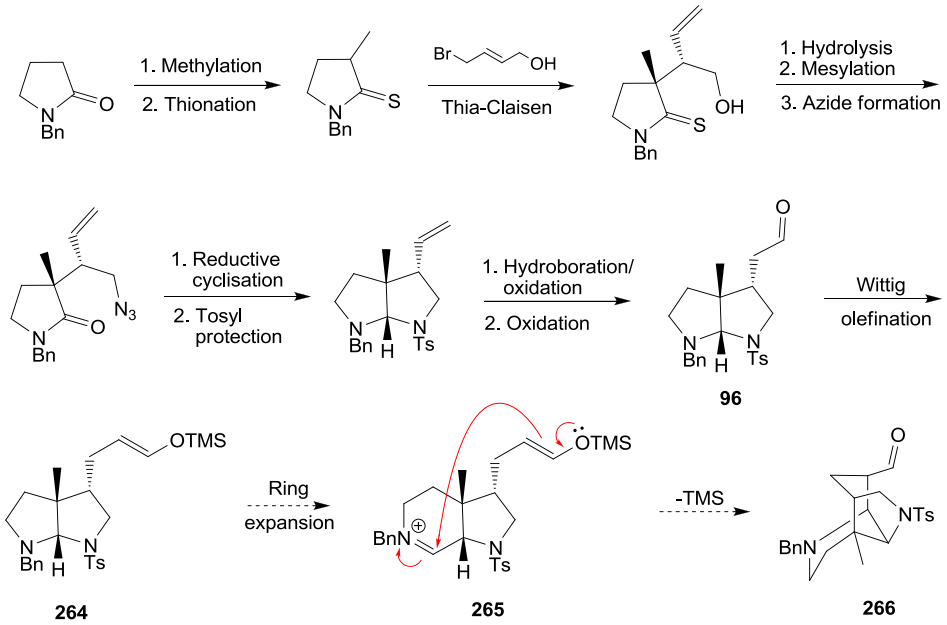


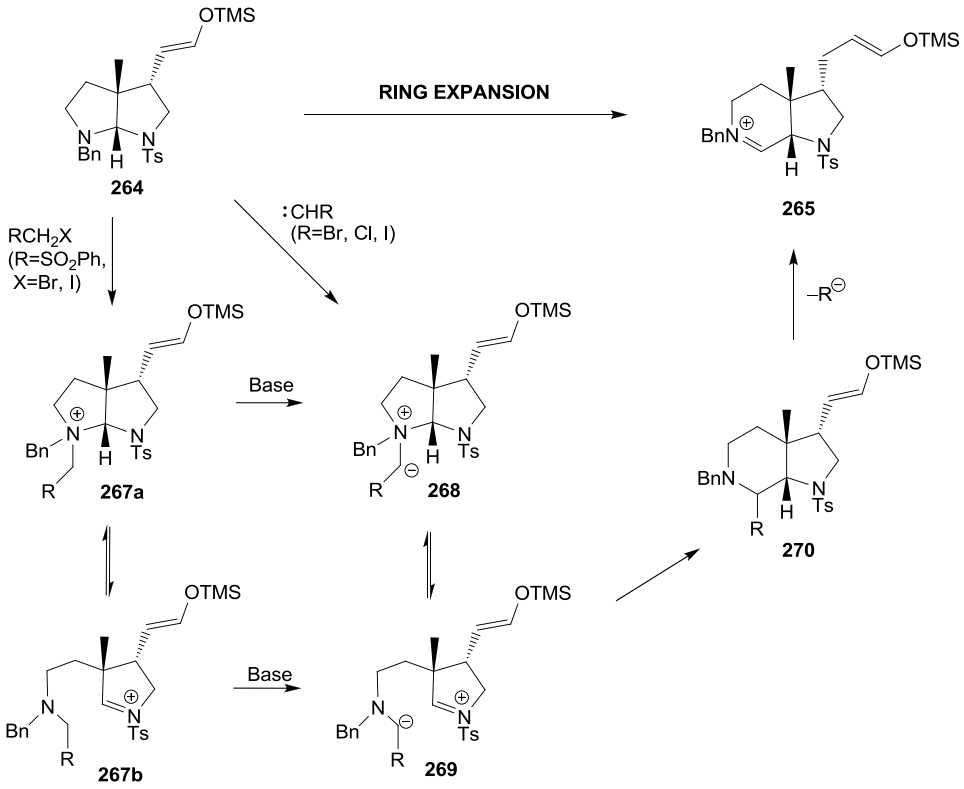
Figure 22 Two strategies towards the sarain core

Detailed below is our proposed synthesis of sarain core **95** via this ring expansion approach. All synthetic steps up to aldehyde **96** are identical to those previously developed within our group (section 1.4.7); however, key aldehyde **96** would then undergo a Wittig olefination reaction to form silyl enol ether **264**, which, following the ring expansion, would cyclise onto the iminium ion in **265** to form sarain core **266** (Scheme 54).



Scheme 54 Ring expansion approach towards the sarain core

The ring expansion step that forms the iminium ion could be achieved in one of two ways. In the first approach, reaction of bicycle **264** with a monohalocarbene would result in alkylation on the more nucleophilic nitrogen (NBn) to form ylide **268**, which could ring open to give iminium ion **269** and subsequently ring close to give 5,6-bicycle **270**; expulsion of the halogen would then form iminium ion **265** (Scheme 55). Dihalocarbenes may also be effective in this chemistry, with the extra halogen being removed subsequently.

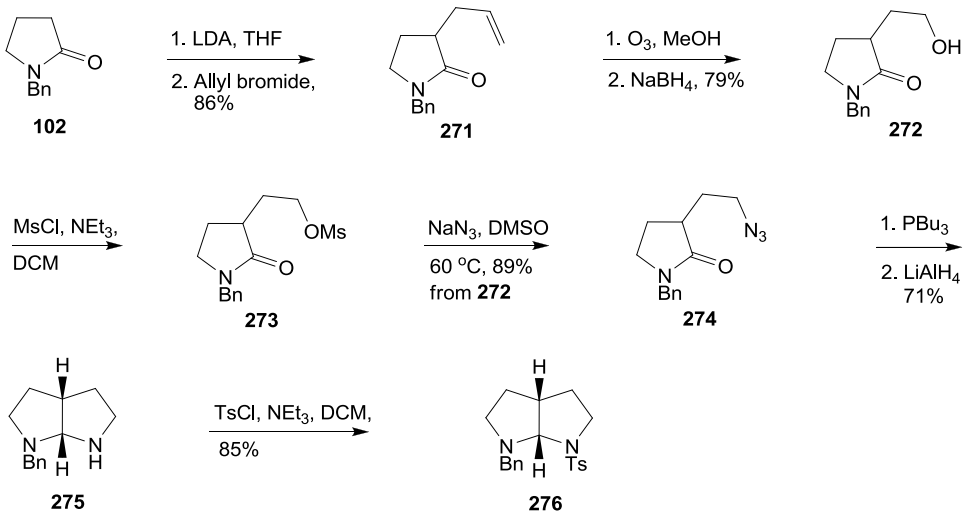


Scheme 55 Ring expansion via two different methods

In the second approach, alkylation of **264** using an alkyl halide on the more nucleophilic nitrogen would lead to alkylated product **267a** which is in equilibrium with amine **267b**; deprotonation of either **267a** or **267b** would lead to **268** or **269** respectively. The same sequence of steps from either of these precursors could then lead to ring expanded product **265** (Scheme 55). This strategy requires the alkyl halide to bear a good leaving group that is also anion-stabilising (e.g. R = sulfonate).

3.1.1 Model substrate formation

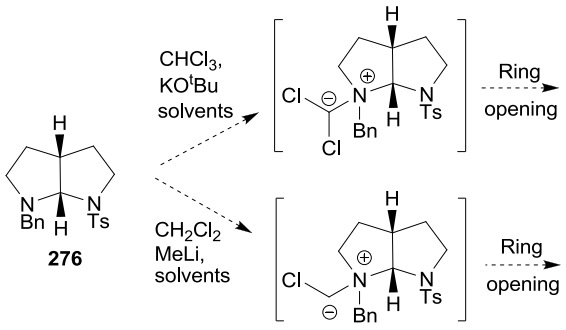
We decided to test the proposed ring expansion step on bicycle **276** (which lacks the side chain of **264**). Bicycle **276** was made in 9 steps from lactam **102**, using a procedure previously developed within the group;[80] the synthesis started with allylation of lactam **102** followed by ozonolysis of the double bond and reduction of the resultant intermediate *in situ* to give alcohol **272**. Alcohol **272** was mesylated and then converted into the corresponding azide **274** using sodium azide. Reductive cyclisation of azide **274** afforded secondary amine **275**, which, upon tosylation gave the required bicycle **276** in 36% overall yield from lactam **102** (Scheme 56).



Scheme 56 Formation of model precursor **276**

3.1.2 Ring expansion step - attempts

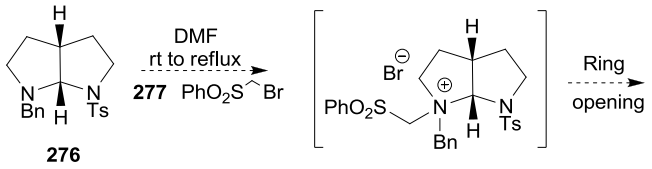
We began our ring expansion attempts by treating model substrate bicycle **276** with two different carbenes: (i) dichlorocarbene (by reaction of chloroform with KO^{t}Bu);[81] (ii) monochlorocarbene (by reaction of dichloromethane with MeLi). However, despite several attempts to perform the alkylation/ring expansion in different solvents and at various temperatures, we were unable to isolate anything other than starting material from all reactions (Scheme 57).



Halogen	Base	Solvent	Temp/°C
$CHCl_3$	KO^{t}Bu	THF Et_2O $CHCl_3$	–30 to 25 25 25
CH_2Cl_2	MeLi	CH_2Cl_2 THF	–35 to 25 –35 to 25

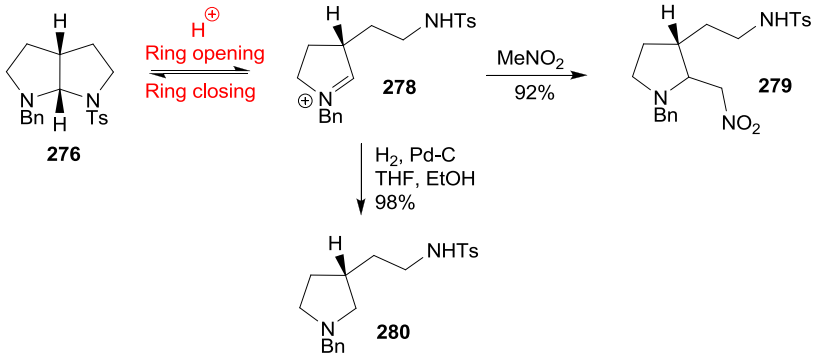
Scheme 57 Attempted ring expansions using carbenes

The ring expansion was next attempted with bromide **277** (Scheme 58). However, once again, the desired alkylation did not occur on any occasion.



Scheme 58 Attempted ring expansions using an alkyl halide

Interestingly, when the above reaction was repeated with nitromethane as the solvent, product **279** was observed. Furthermore, when bicycle **276** was simply stirred in nitromethane alone, the same product was formed. We believe that this product arises due to bicycle **276** fluctuating between its ring-opened and ring-closed state; as a result, when the reaction is performed in nitromethane, a nitro-Mannich reaction can occur to trap iminium ion **278** and give rise to product **279** (Scheme 59, right).

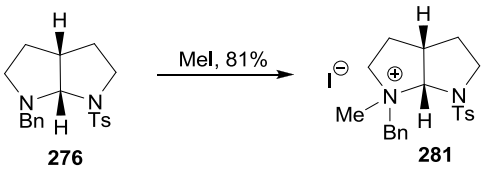


Scheme 59 Nitro-Mannich reaction and hydrogenation of iminium ion

In order to improve the chance of alkylation occurring on the desired nitrogen in bicycle **276**, a debenzylation was attempted to produce an unprotected secondary amine.[82] However, when bicycle **276** was treated with standard hydrogenation conditions, amine **280** was isolated. This result can be explained as being a result of hydrogenation of intermediate iminium ion **278** that is formed when the ring opens (Scheme 59). Debenzylation was also attempted using CAN in an acetonitrile and water mixture; however, only starting material was obtained from this reaction.[83]

Although it was clear that the ring expansion strategy was not a viable way in which we could form the sarain core due to the non-nucleophilicity of the benzylated nitrogen atom, we were interested to see whether the nitrogen atom could be alkylated using alternative halides, even if they would not generate a product that could be transformed into the sarain core in subsequent steps. To this end, bicycle **276** was treated with neat

iodomethane at room temperature, and alkylated product **281** was indeed isolated in 81% yield (Scheme 60).



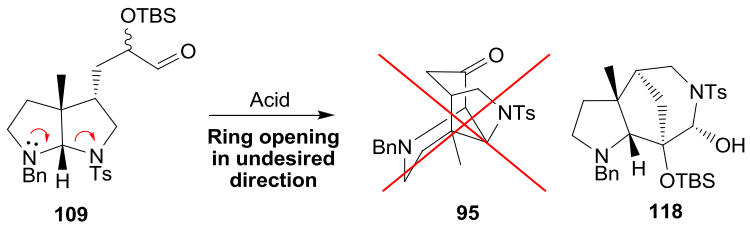
Scheme 60 Methylation of sarain intermediate

This step indicated that the desired nitrogen could be alkylated, however, only with exceptionally good electrophiles such as iodomethane.

3.2 Protecting group reversal strategy towards the sarain core

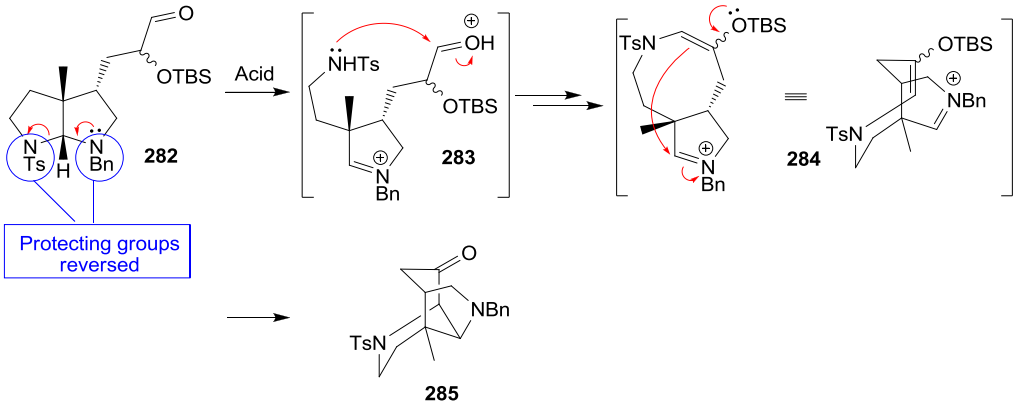
3.2.1 Strategy

As described in section 1.4.7, previous members of the Porter group have attempted to form sarain core **95** via an acid catalysed ring opening/cyclisation.[28] However, this route failed as in the key final step bicycle **109** opened in the undesired direction and led to the formation of tricycle **118** (Scheme 61).



Scheme 61 Previous attempted acid catalysed ring opening/cyclisation to form the sarain core

In light of this result, we speculated that by switching the protecting groups around on the bicycle (i.e. to give bicycle **282**), the ring opening step may occur in the *desired* direction, hence enabling the formation of the sarain core (Scheme 62).

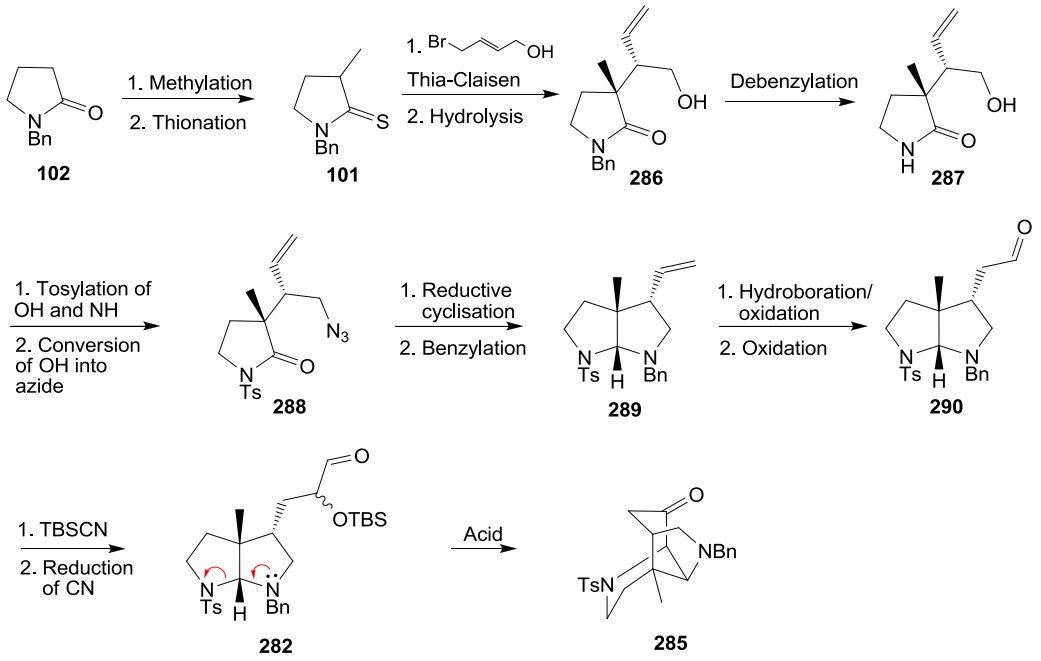


Scheme 62 Proposed acid catalysed route towards the sarain core

Upon ring opening, secondary sulfonamide **283** would result; this would then attack the protonated aldehyde group to form 8-membered ring **284** which, following intramolecular attack of the silyl enol ether onto the iminium ion, would form sarain core **285**.

3.2.2 Proposed synthetic route

A detailed synthetic strategy of our revised route towards the core is shown below (Scheme 63). We planned to use the chemistry previously developed by the group to synthesise lactam **286** and thus, the thia-Claisen rearrangement would still be the key step that provides the correct relative stereochemistry that is present in lactam **286**; at this stage, we planned not to use the asymmetric thia-Claisen rearrangement discussed in the previous chapter until a full route towards the sarain core had been developed.



Scheme 63 Proposed approach towards the sarain core

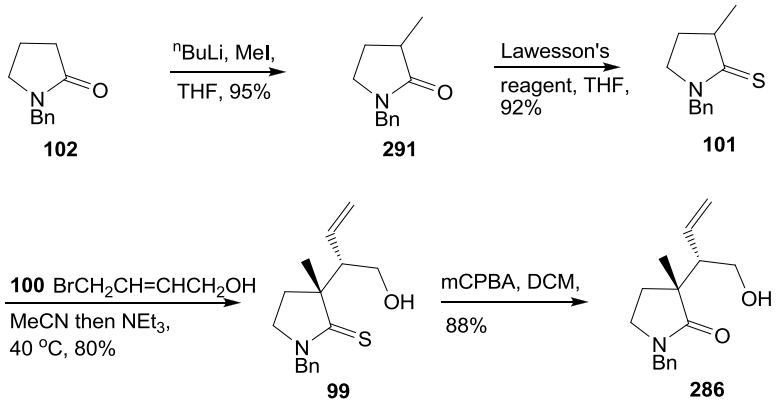
The first step that differs from our previous method is a debenzylation of lactam **286** to afford lactam **287**. Following this, both the OH and NH groups of **287** would be converted to their *p*-toluenesulfonyl derivatives, and the tosylate displaced to form azide **288**. The reductive cyclisation step to form the bicyclic system could then be performed, according to the precedent from earlier work; the resulting secondary amine would be protected with a benzyl group to give alkene **289**. At this stage we would have successfully interchanged the protecting groups on the nitrogen atoms compared with previous routes.

All that would remain would be to convert alkene **289** into aldehyde **290** via the corresponding alcohol, and reaction of this aldehyde with TBSCN, followed by reduction of the nitrile would give rise to aldehyde **282**. This key precursor would be treated with acid in an attempt to convert it into sarain core **285** in the fashion described in Scheme 62.

3.2.3 Early steps

The synthesis started with methylation of lactam **102**, followed by thionation using Lawesson's reagent to give thiolactam **101** in 87% over the two steps. Following this, the thia-Claisen rearrangement was performed; alkylation of thiolactam **101** with allylic bromide **100** (made from reduction of ethyl-4-bromocrotonate using DIBAL, in 77%

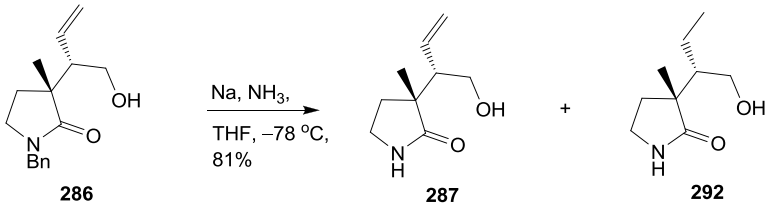
yield) followed by treatment with triethylamine gave alcohol **99** in 80% yield. Thiolactam **99** was then hydrolysed using *m*CPBA to give lactam **286** in 88% yield (Scheme 64).



Scheme 64 Early steps towards the sarain core[28]

3.2.4 Debenzylation of *N*-benzyl lactam

Debenzylation of the nitrogen atom in lactam **286** was required so that a tosyl protecting group could be introduced at a later stage. To this end, *N*-benzyl lactam **286** was subjected to dissolving metal reduction using 5 equivalents of sodium in liquid ammonia.[84] Although these conditions were effective in removing the benzyl group from the nitrogen atom to form amide **287**, a considerable amount of alkene reduction was also observed, giving alcohol **292** as a by-product (Scheme 65).

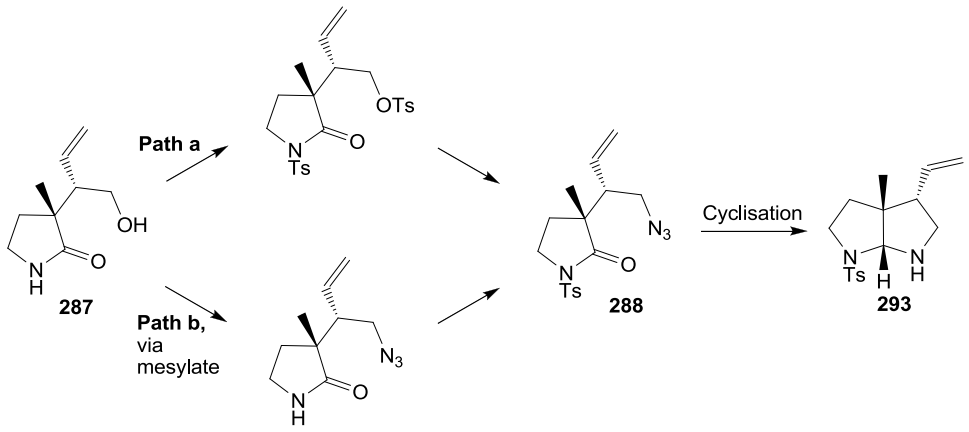


Scheme 65 Debenzylation of lactam **286**

However, after reaction optimisation, it was found that by reducing the amount of sodium metal to 2 equivalents and stirring the mixture for only 5-15 minutes, unprotected lactam **287** could be routinely isolated as the sole product in good yields.

3.2.5 Formation of *N*-tosyl bicycle

The next hurdle that had to be overcome was the conversion of lactam **287** into *N*-tosyl bicycle **293** (Scheme 66). This conversion could conceivably be achieved in one of two ways: (i) via tosyl protection of the OH and NH moieties in the molecule and displacement of the tosylate to give azide **288** – path a; (ii) via conversion of the alcohol into the corresponding azide, via the mesylate, followed by tosylation of the remaining nitrogen atom – path b.



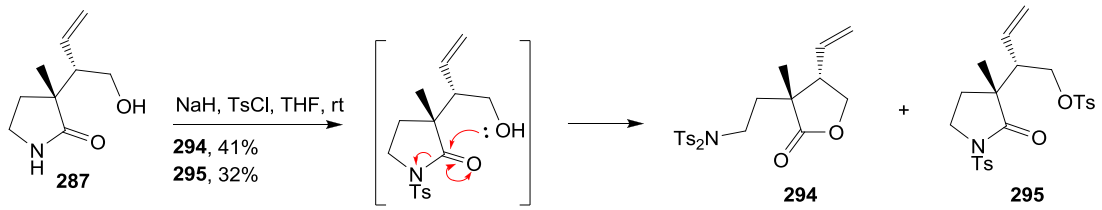
Scheme 66 Possible pathways towards bicycle **292**

It was important that the nitrogen atom in lactam **288** was protected *prior* to the cyclisation (i.e. the sequence of steps towards bicycle **293** had to go via azide **288**), otherwise a bicycle with two unprotected nitrogen atoms would be formed, each requiring different protecting groups.

3.2.5.1 *N*-Tosyl protection before azide formation

We first attempted tosylation of both the lactam nitrogen and the alcohol of **287** in one step; the alcohol group was to be converted into the corresponding azide in the following step and so a good leaving group on the oxygen was required. Thus, lactam **287** was treated with 2.2 equivalents of sodium hydride in THF, followed by the addition of excess tosyl chloride. The desired bis-protected product **295** was isolated, but was accompanied by undesired lactone **294** (Scheme 67). Lactone **294** was thought to have arisen due to protection on nitrogen happening first and then cyclisation of the alcohol onto an *N*-protected lactam. This cyclisation occurs readily because the sulfonamide protecting group is electron withdrawing and hence renders the carbon centre of the lactam very electrophilic and susceptible to attack from the nearby alcohol

(*cf*. previous routes where the lactam nitrogen bears a benzyl group –Scheme 16, section 1.4.7).



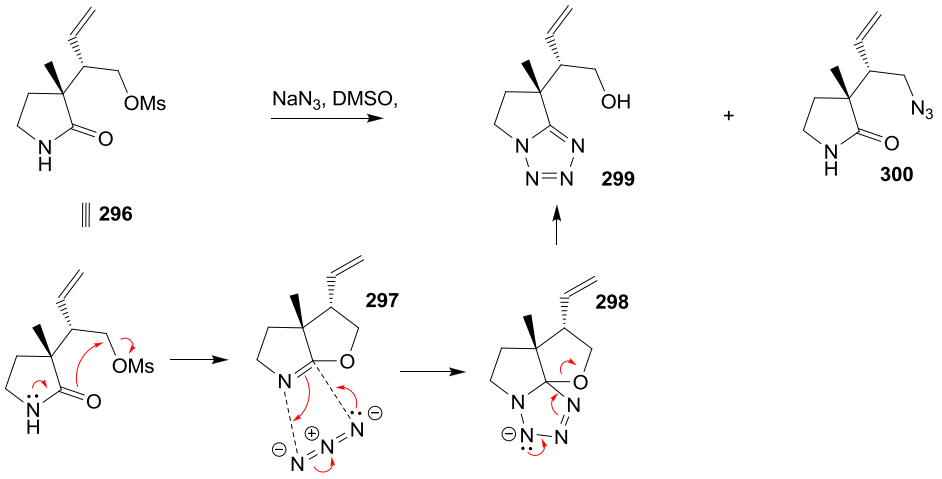
Scheme 67 Attempted formation of di-tosylated product **295**

3.2.5.2 Azide formation before *N*-tosylation

We next decided to use a mild mesylation procedure to convert alcohol **287** into the corresponding mesylate, and then following conversion to the azide, the nitrogen atom would be protected. Hence, alcohol **287** was treated with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature; pleasingly, mesylate **296** was isolated in very good yield with no trace of the equivalent lactone by-product that is shown in Scheme 67.

Scheme 68 Mesylation of alcohol

The next step in our synthesis involved conversion of mesylate **296** into azide **300**. Thus, mesylate **296** and sodium azide were dissolved in DMF and the solution stirred at 60 ºC. Despite the usual reliability of this reaction when used on other substrates,[28,29] in this case we obtained a 1:1 mixture of azide **300** and tetrazole **299** (Scheme 69 and Table 4, entry 1).



Scheme 69 Attempted azide formation; formation of tetrazole **299**

Tetrazole **299** was believed to have formed in this case as the unprotected lactam (which is more nucleophilic than its *N*-benzylated equivalent – see Scheme 16, section 1.4.7) is able to attack the nearby carbon centre in an intramolecular fashion to form intermediate **297**, which then undergoes a [3+2] cycloaddition with the azide anion to form tricycle **298**; this then ring opens to form tetrazole **299**.[85] To thwart this process, we first increased the NaN_3 loading from 3 equivalents up to 5; it was believed that excess azide may force the desired reaction to happen faster than the undesired intramolecular cyclisation. Indeed, this increased the azide **300**:tetrazole **299** ratio to 5:1 (entry 2, Table 4).

After studying the effect of concentration on the ratio of azide **300** to tetrazole **299** (entry 3), we then tried altering the reaction temperature and the order that the reagents were added (entries 4-7, Table 4).

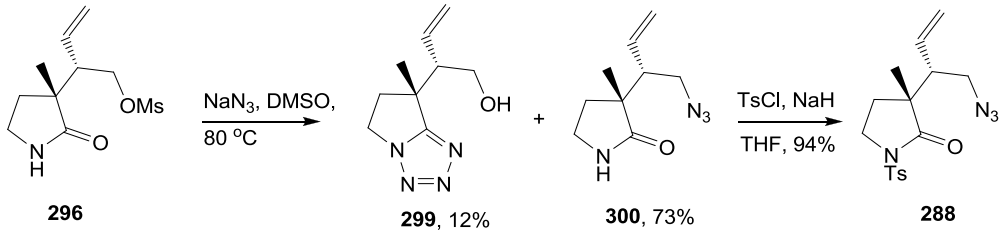
Entry[a]	Temp / °C	Equiv. NaN_3	Ratio **300**:**299**[e]
1	60	3	1:1
2	60	5	5.0:1
3[b]	60	5	2.4:1
4	40	5	3.5:1
5	80	5	6.4:1
6[c]	80	5	3.1:1
7[d]	80	5	7.3:1

[a] Reactions conducted at 0.1 M concentration of **296**; the solution was at rt until all reagents were added, followed by heating to the specified temperature. [b] 0.2 M concentration of **296.** [c] Solution of mesylate in DMF was preheated prior to addition of NaN_3. [d] Solution of sodium azide in DMF was preheated prior to addition of mesylate **296**. [e] Ratio determined by ^{1}H NMR analysis.

Table 4 Optimisation of azide formation step

It was found that decreasing the temperature promoted tetrazole formation (entry 4) and conversely, increasing the temperature to 80 ºC encouraged azide formation (entry 5). In light of this result, we attempted the reaction at 80 ºC with: (i) a preheated solution of mesylate in DMF (entry 6) and (ii) a preheated solution of sodium azide in DMF (entry 7). As expected, the reaction which involved preheating a solution of mesylate **296** in DMF gave more tetrazole product (as intermediate **297** would begin forming before NaN_3 is added) and the preheated solution of sodium azide in DMF gave an increased ratio of azide to tetrazole (i.e. there is no occasion where intermediate **297** can form without competition from the azide forming step).

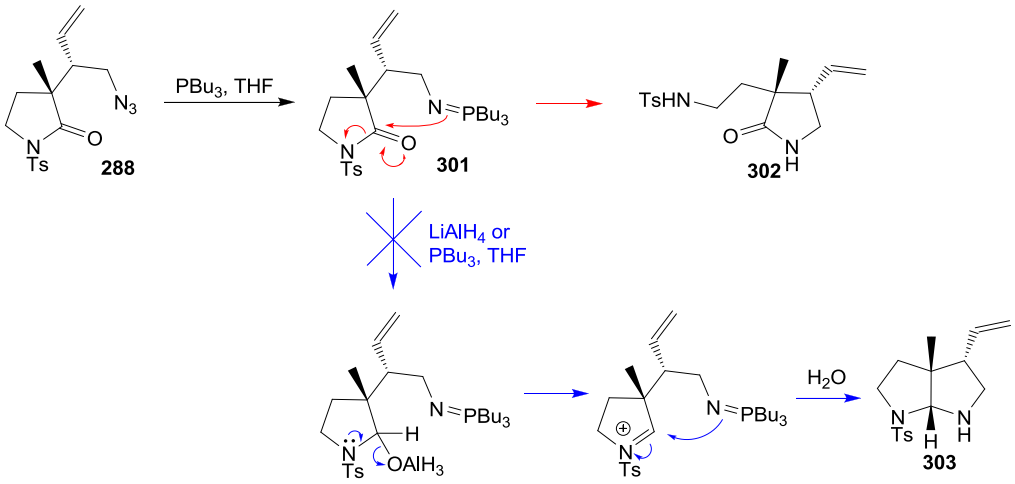
After the optimisation described above, the conditions that we employed for the azide formation step were those of entry 7; azide **300** was obtained in 73% yield along with 12% of tetrazole **299**. The unprotected lactam moiety in azide **300** was subsequently sulfonylated with ease using sodium hydride as a base to give *N*-tosyl lactam **288** in excellent yield (Scheme 70).



Scheme 70 Two step conversion of lactam **296** into azide **288**

3.2.6 Reductive cyclisation and benzyl protection

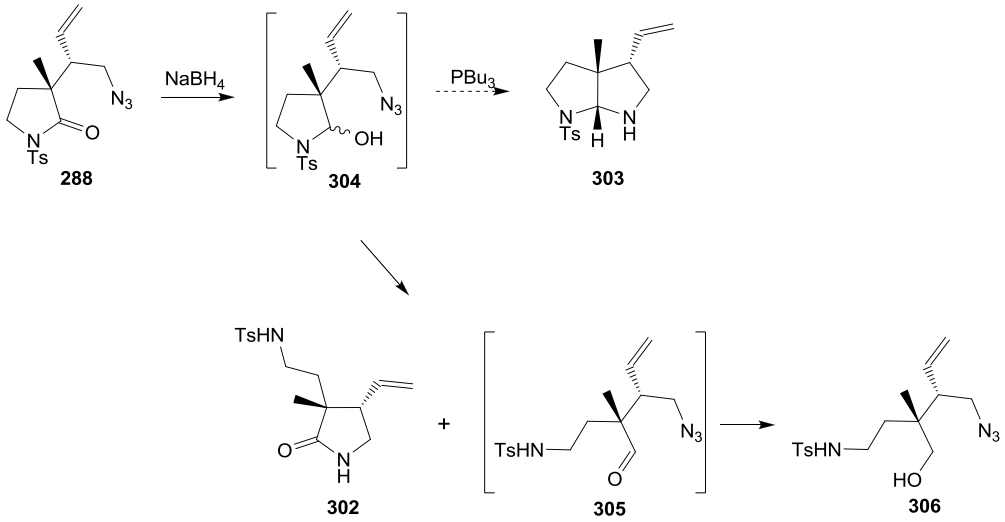
The group's previous methods towards the core (Scheme 14, section 1.4.7) involved a reductive cyclisation step that uses tri-*n*-butylphosphine followed by lithium aluminium hydride. When these conditions were used on azide **288**, lactam **302** formed very quickly after the addition of tri-*n*-butylphosphine (by TLC analysis) and did not disappear after the addition of lithium aluminium hydride. Unsurprisingly, simple addition of tri-*n*-butylphosphine to a mixture of azide **288** and THF gave the same result (Scheme 71).



Scheme 71 Attempted reductive cyclisation; formation of lactam **302**

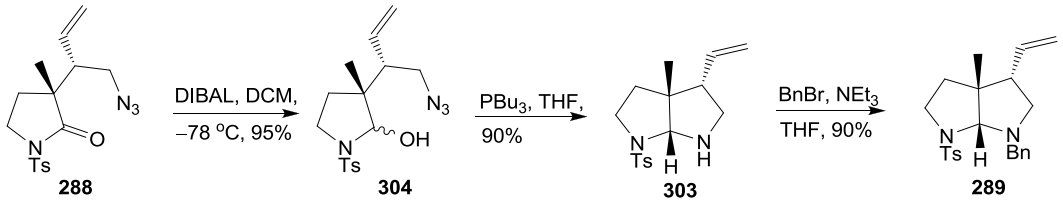
It was believed that intermediate **301** formed upon addition of tri-*n*-butylphosphine as desired. However, due to the high electronegativity of the tosyl-lactam carbon in **301**, intramolecular attack from the iminophosphorane moiety occurs to generate lactam **302** *before* lithium aluminium hydride is added to the reaction (Scheme 71).

In an attempt to circumvent this problem, we targeted the formation of an intermediate such as aminal **304** before reduction of the azide. With intermediate **304** synthesised, subsequent reduction of the azide would provide the desired bicycle. Thus, reduction of the lactam moiety in **288** to hemiaminal **304** was attempted using sodium borohydride; (Scheme 72). However, formation of hemiaminal **304** was followed by spontaneous ring opening to give aldehyde **305**, which was further reduced to alcohol **306**. In addition, lactam **302** was isolated; this presumably arises through reduction of the azide to the amine followed by cyclisation to form the lactam ring (Scheme 72).



Scheme 72 Attempted reduction of lactam to *N*,*O*-acetal using $NaBH_4$

We next attempted the reduction using DIBAL.[86] Gratifyingly, upon treatment of azide **288** with 1.2 equivalents of DIBAL in dichloromethane, hemiaminal **304** was isolated in very good yield as a mixture of diastereoisomers (Scheme 73). Ring cyclisation was then performed by reaction of hemiaminal **304** with tri-*n*-butylphosphine to give bicycle **303** in 90% yield.



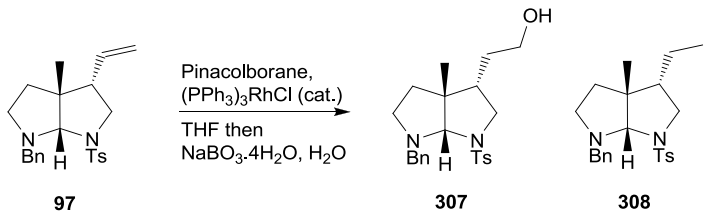
Scheme 73 Formation of bicycle **289** via hemiaminal **304**

Finally, bicycle **303** was *N*-protected with a benzyl group to give di-protected bicycle **289** with the correct arrangement of the two protecting groups (i.e. opposite to that used in previous route).

3.2.7 Hydroboration/oxidation of alkene

3.2.7.1 Previous strategy employed by the Porter group

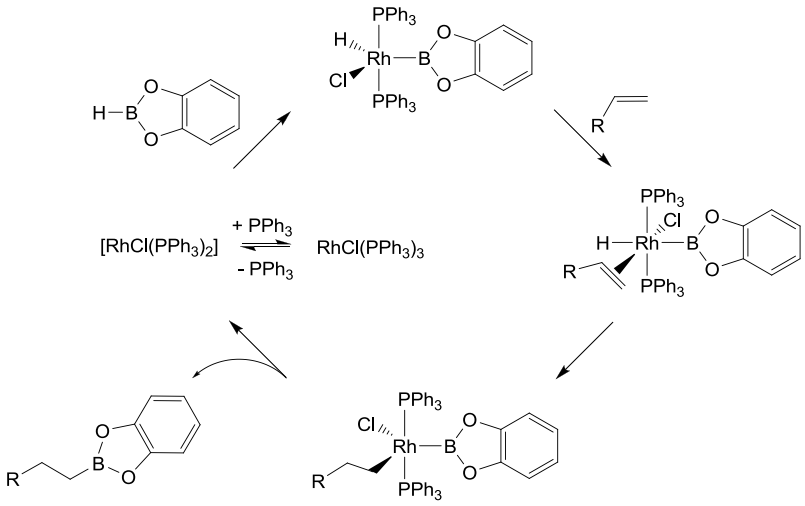
The previous strategy adopted by our group on an analogous transformation (Scheme 74) involved reaction of alkene **97** with Wilkinson's catalyst and pinacolborane in THF; attempts that used BH_3.THF and 9-BBN were unsuccessful.[28,87] A one-pot procedure whereby the intermediate boronate was not isolated, but instead converted directly into alcohol **307** using sodium perborate was found to be highest yielding. However, in all cases, product **307** was accompanied by an appreciable amount of over-reduced product **308** (up to 27%).



Scheme 74 Previous strategy adopted by the group for hydroboration/oxidation reaction

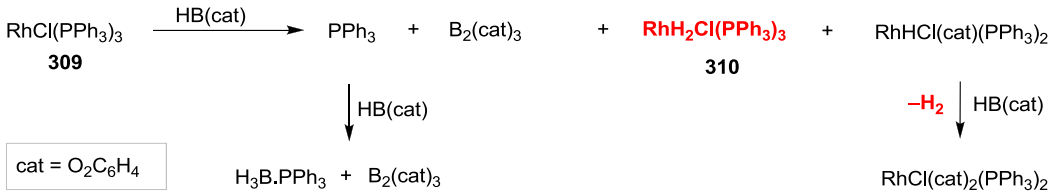
A proposed mechanism for the hydroboration of an alkene with the related catecholborane and Wilkinson's catalyst shows the reaction to involve oxidative

addition of the B-H bond to Rh(I), alkene insertion into the Rh-H bond and finally, reductive elimination of the B-C bond to give the boronate product (Scheme 75).[88]



Scheme 75 A possible mechanism for alkene hydroborations mediated by Wilkinson's catalyst

In this detailed study, Burgess also states that mixing of Wilkinson's catalyst **309** and catecholborane alone (i.e. in the absence of an alkene) results in significant degradation of catecholborane, giving rise to a number of products (Scheme 76). The most significant of these are thought to be dihydride complex **310**, a known catalyst for hydrogenation reactions, and H_2 itself (the source of **308**); we assume that something similar might happen with pinacolborane, although to our knowledge this study has never been carried out. In addition, Wilkinson's catalyst is known to undergo oxidation, especially when in solution, and the resulting oxidised catalyst is thought to be a more potent hydrogenation catalyst.[89]

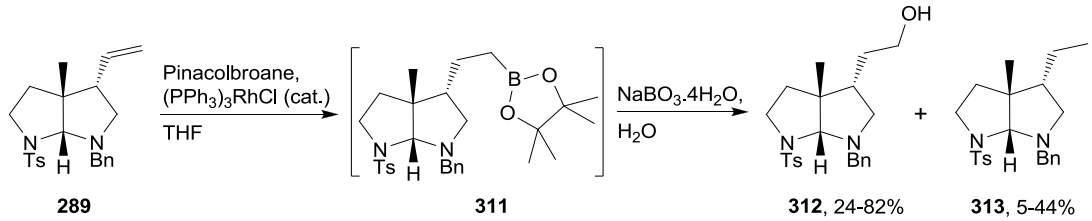


Scheme 76 Reaction of Wilkinson's catalyst with catecholborane

With this information in hand, the Porter group decided to repeat the reaction shown in Scheme 74 with thorough degassing of the solution to reduce this oxidation effect. Pleasingly, an increased ratio of **307**:**308** and yield of alcohol **307** was obtained (86%).

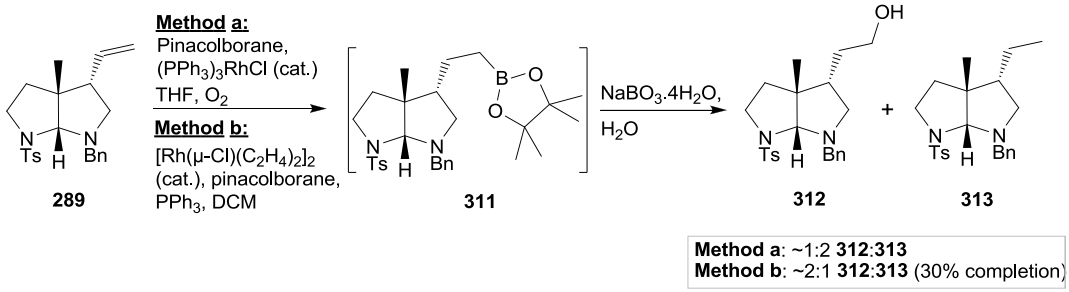
3.2.7.2 Work on current alkene

When these reaction conditions were used on bicycle **289**, alcohol **312** was obtained in up to 82% yield (via boronate **311**), with a small amount of reduced product **313** obtained (Scheme 77). However, on repetition, the reaction was found to be capricious; a low ratio of alcohol **312** to reduced product **313** (up to 1:2 **312**:**313**) was commonly obtained and hence an alternative, more reliable procedure for this transformation was sought.



Scheme 77 Hydroboration/oxidation of alkene using Wilkinson's catalyst

We next attempted the reaction using a procedure described by Crudden *et al*. whereby a stream of air was passed through the reaction mixture (Scheme 78);[90] although this contradicts with the procedure previously used (Scheme 77), the authors claim that a much improved alcohol to reduced product ratio can be obtained using this method. However, when this protocol was implemented on alkene **289**, no improvement on the ratio was observed.



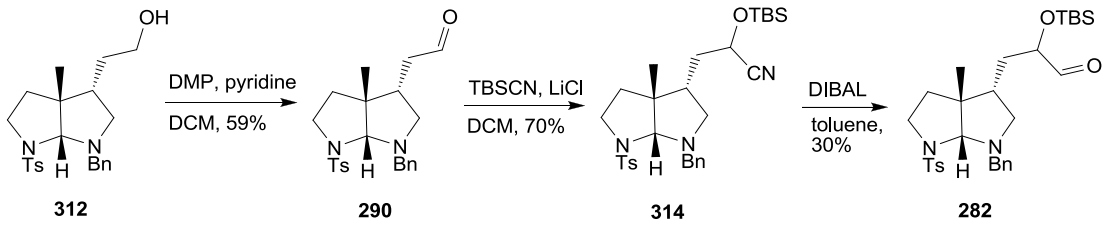
Scheme 78 Alternative attempts at hydroboration/oxidation step

In the same paper, Crudden and co-workers also use an alternative catalyst, [Rh(μ-Cl)$(C_2H_4)_2]_2$, in the presence of triphenylphosphine, to perform their hydroboration step; use of this catalyst was found to give more consistent results. However, in our case, this procedure only converted 30% of the starting material to product after 4 days of stirring and did not increase the ratio of **312**:**313**.

At this stage, we decided to continue with our route towards the core using the original method for hydroboration/oxidation shown in Scheme 77, even though the yields obtained were variable; several grams of alcohol **312** was obtained.

3.2.8 Final stages towards the sarain core

The final stages towards the sarain core began with oxidation of alcohol **312** to give aldehyde **290** using Dess-Martin periodinane and pyridine in 59% yield (Scheme 79); following this, addition of TBSCN gave desired nitrile **314** in 70% yield. Finally, DIBAL reduction of nitrile **314** gave the required rearrangement precursor **282** in a disappointingly low yield (up to 30%).

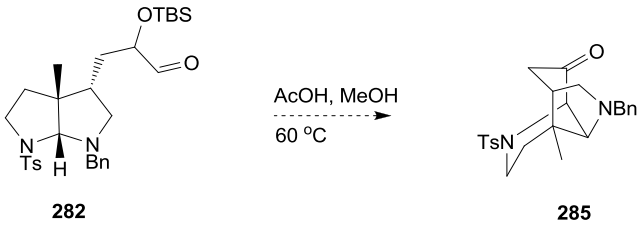


Scheme 79 Final steps towards rearrangement precursor [27]

Although this sequence of steps was capable of providing a small quantity of aldehyde **282**, the low yields obtained (in addition to the troublesome step depicted in Scheme 77) prevented any significant quantity of aldehyde **282** from being synthesised.

3.2.9 Attempted rearrangement to give the sarain core

The key rearrangement step was attempted only once on a 7 milligram scale, due to lack of material and time constraints. The conditions used were the same as those that were previously employed by the Porter group,[28] which had given some success on a similar substrate. Unfortunately, there was no indication that sarain core **285** had formed from analysis of the crude ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the crude reaction mixture indicated that several products were formed, and there was no evidence for the formation of **285**.



Scheme 80 Attempted rearrangement to give sarain core **285**

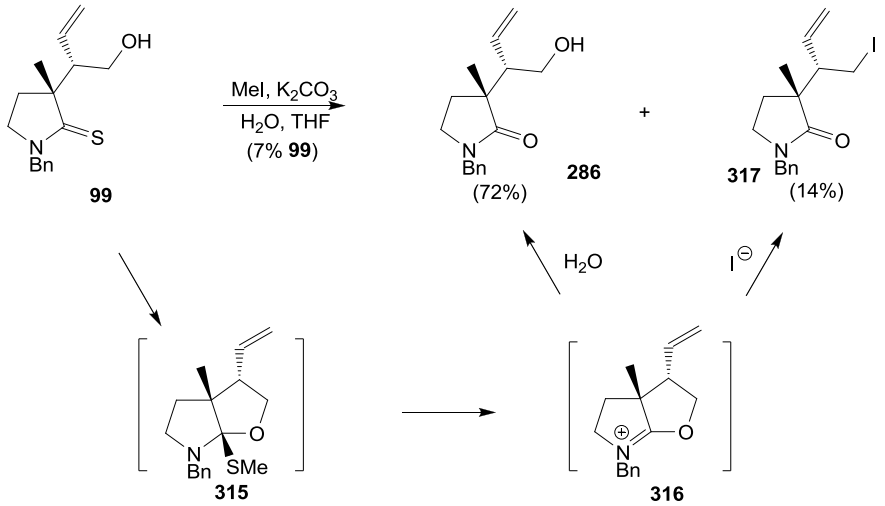
It must be noted that although this reaction did not proceed as we desired, more success may have been obtained if the reaction was done on a larger scale with a more manageable amount of starting material and solvent (the small amount of AcOH/MeOH used in the reaction evaporated after a few hours at 60 ºC).

4 A new method for alcohol activation

4.1 Alcohol iodination[91]

4.1.1 Iodination studies on an intermediate en route to sarain A

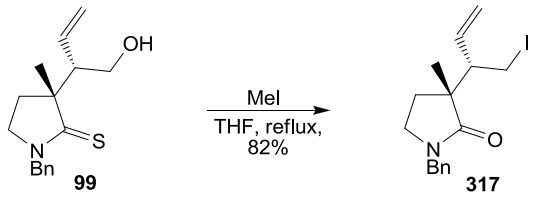
Previous work in the Porter group has revealed that hydrolysis of thiolactam **99** using methyl iodide in mild aqueous base generates the expected alcohol **286**, as well as a small amount of iodide **317** (Scheme 81).[28] This undesired side-reaction prompted the group to adopt a different strategy in order to hydrolyse thiolactam **99**; namely, using *m*CPBA (Scheme 64). Despite this result being undesired, the nature in which iodide **317** had formed from **99** warranted further investigation.



Scheme 81 Attempted hydrolysis of thiolactam **99**; the formation of iodide **317**

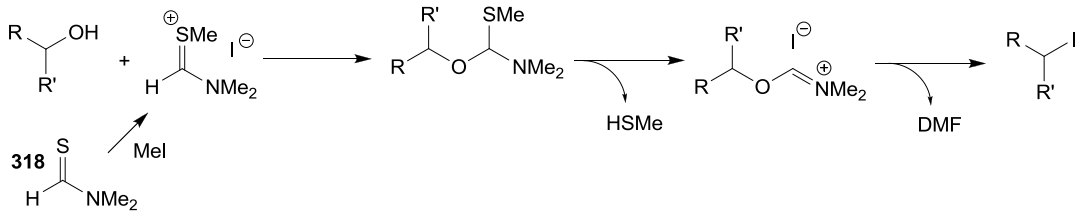
The products from this reaction were thought to arise through initial methylation of the sulfur atom, cyclisation of the alcohol to form intermediate **315**, and following expulsion of methanethiol (or, following a second methylation, dimethyl sulfide), iminium ion **316** could undergo either hydrolysis to form alcohol **286**, or nucleophilic attack by an iodide ion to generate iodide **317**.

We anticipated that exclusion of water from the reaction mixture would enhance formation of iodide **317**. Hence, alcohol **99** was treated with two equivalents of methyl iodide in THF at reflux for two days (Scheme 82). Pleasingly, iodide **317** was generated in 82% yield, with no trace of alcohol **286** being formed.



Scheme 82 Iodination of sarain A intermediate **99** using MeI

With this intramolecular one-step conversion of alcohol/thioamide **99** into iodide/amide **317** a success, it seemed plausible that if an alcohol was treated with a methylated thioamide *inter*molecularly in the absence of water, it may be possible to convert a range of alcohols into iodides in a similar fashion. Moreover, if the thioamide chosen was *N*,*N*-dimethylthioformamide (**318**), the by-products expelled from the reaction would be the readily removable DMF and methanethiol (Scheme 83).



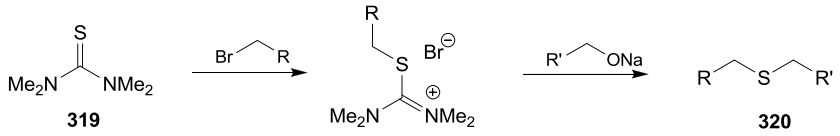
Scheme 83 Proposed transformation of alcohol to iodide using a thioamide derived salt

4.1.2 Iodination of alcohols: related literature

A wide range of procedures are known for the direct conversion of alcohols into iodides; however, most of these procedures are based on phosphorus chemistry,[92] for example PPh_3/I_2/imidazole,[93] PPh_3/NIS,[94] PPh_3/DEAD/MeI[95] and $P(OPh)_3$/MeI.[96,97] All of the aforementioned procedures produce phosphine oxides or phosphonates as by-products, often resulting in difficult workup procedures and product isolation. In addition, separation of polar iodides from the phosphine oxide by-products can be difficult even after column chromatography.

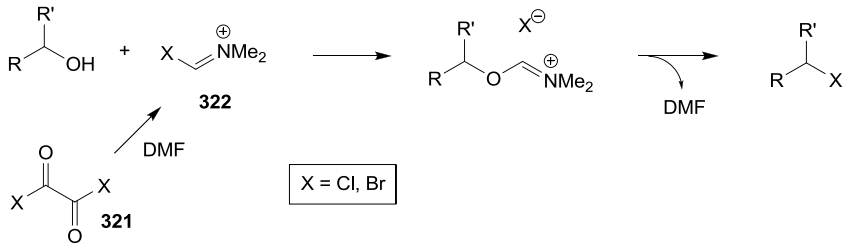
Other reagents that have been used for this transformation include BF_3-Et_2O/KI,[98] P_4/I_2,[99] Cl_2SO–DMF/KI,[100] MgI_2,[101] $ClSiMe_3$/NaI,[102] PBu_3I_2/C_6H_6/HMPA[103] and $CeCl_3.7H_2O$/KI.[104] However, such procedures commonly suffer from one or more of the following problems: low yields, long reaction times, harsh reaction conditions, tedious workup procedures, low functional group compatibility and non-commercially available reagents.

There is some precedent for our proposed iodination method. The use of *S*-alkylated thioureas for the activation of alcohols has been studied by Kajigaeshi *et al*., where *N*,*N*,*N*',*N*'-tetramethylthiourea (**319**) was reacted with the alkyl bromide and subsequently a sodium alkoxide was added to generate an unsymmetrical sufide **320** (Scheme 84).[105]



Scheme 84 Preparation of unsymmetrical sulfides

Further related precedent comes from the reaction of alcohols with haloiminium halide **322**, to give an alkyl halide (Scheme 85).[106,107,108] The haloimium salts required for these transformations are formed from reaction of DMF and oxalyl halide (**321**). However, this reaction is not amenable to the synthesis of iodoalkanes.

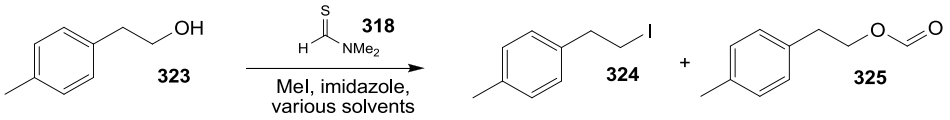


Scheme 85 Formation of haloalkanes with haloiminium salts **322**

4.1.3 Results: Intermolecular iodination of alcohols

4.1.3.1 Solvent Screening

Initial iodination studies employed *para*-methylphenethyl alcohol (**323**) as a test substrate. Upon treatment of alcohol **323** with two equivalents of thioamide **318** and four equivalents of MeI in various solvents at elevated temperatures, all reactions produced some iodide **324** but failed to go to completion within 24 hours. However, addition of 2 equivalents of imidazole significantly increased the rate, enabling the iodination to be screened in a selection of common solvents (Scheme 86; Table 5). The role of the imidazole is not entirely clear, as it could act as a base or as a nucleophilic catalyst.



Scheme 86 Solvent screening for iodination of a primary alcohol

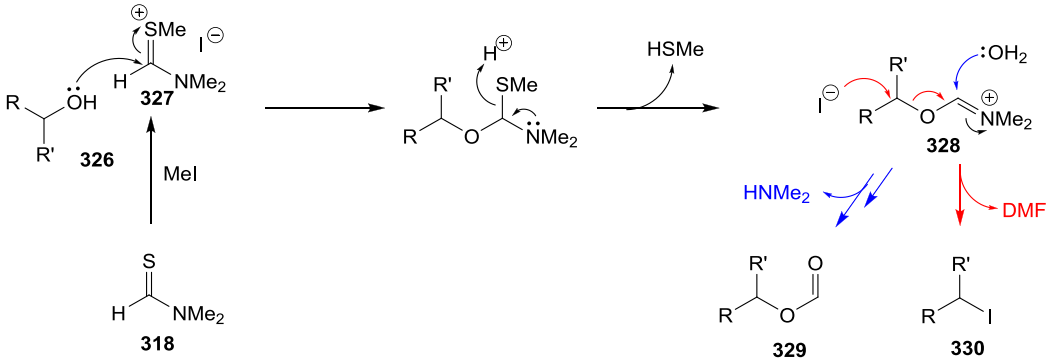
Entry[a]	Solvent	Conversion to products / %	Ratio of products[b] Iodide **324**:formate **325**
1	THF	100	11.0:1
2	CH_2Cl_2	100	5.9:1
3	Et_2O	39	1:3.6
4	toluene	92	11.0:1
5	MeCN	96	10.5:1
6	DMF[c]	5	0:1

[a] Conditions: 2 equiv. thioamide **318**, 4 equiv. MeI, 2 equiv. imidazole, reflux, 4 h. [b] Conversion and ratio determined from integration of crude ^{1}H NMR spectra. [c] Reaction conducted at 120 °C.

Table 5 Screening of solvents for iodination reaction

In addition to the desired iodide **324**, formate **325** was generated as a by-product in all cases (entries 1-6, Table 5). The most selective reactions affording iodide **324** relative to formate **325** were observed with THF, toluene or MeCN as the solvent, giving ratios of approximately 11:1 iodide **324**:formate **325** (entries 1, 4 and 5 respectively). Interestingly, with DMF as the solvent, the reaction was extremely slow and formate **325** was the only product observed.

Formate **325** was thought to arise through hydrolysis of alkoxyiminium ion **328** by adventitious water (Scheme 87).[106,109,110] In an attempt to suppress formation of formate **325**, various drying agents (molecular sieves, magnesium sulfate, magnesium oxide) were added to the reaction. However, none were successful in preventing formation of formate **325**.

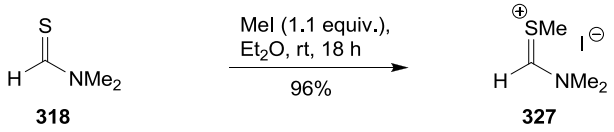


Scheme 87 Proposed mechanism for conversion of alcohol **326** into iodide **330** and formate **329**

At this stage we decided to continue with optimisation of the reaction as we did not believe that the small amount of formate by-product formed would have any detrimental effect on the yield; further insight into the source of the formate by-product was gained subsequently (see section 4.1.3.4).

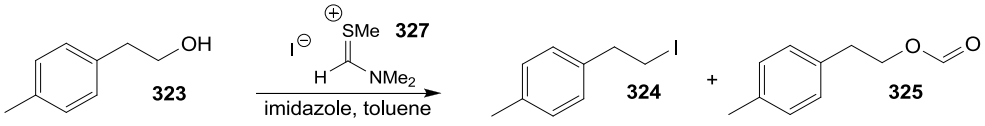
4.1.3.2 Optimisation

Next, the possibility of pre-forming salt **327**, rather than forming it *in situ* was considered. It was believed a cleaner reaction should result, and undesired side-reactions should decrease due to the reduced number of excess electrophilic and nucleophilic reagents present in the reaction mixture. Furthermore, a pre-formed salt would simplify the procedure significantly. Salt **327** was formed by stirring a mixture of *N*,*N*-dimethylthioformamide (**318**) and methyl iodide in anhydrous ether overnight (Scheme 88). Upon completion, the solid (which precipitates from the reaction mixture) was filtered, washed and dried thoroughly, giving a white crystalline salt **327** in excellent yield, which was then stored at –25 °C.



Scheme 88 Formation of salt **327**

Gratifyingly, when salt **327** was employed in the reaction shown in Scheme 86 instead of thioamide **318** and iodomethane, the reaction was still effective (Table 6, entry 1). As a result, it was decided to optimise the iodination using pre-formed salt **327**, toluene as the solvent and alcohol **323** as the test starting material. Table 6 summarises the optimisation studies. Initially, 1.5 equivalents of salt **327** and 1 equivalent of imidazole were used. The reaction was complete in 90 minutes at 85 °C, with a good ratio of iodide **324**:formate **325** being achieved (Scheme 89; Table 6, entry 1). Reducing the amount of imidazole present was not detrimental to the conversion of the reaction; however with 0.25 equivalents of imidazole the reaction was slightly slower (entries 2 and 3).



Scheme 89 Optimisation of iodination conditions

Entry	Equiv. salt **327**	Equiv. imidazole	Temp/°C	Time/h	Conversion to products/%	Ratio of Products[a] **324**: **325**
1	1.5	1	85	1.5	100	12:1
2	1.5	0.5	85	1.5	100	13:1
3	1.5	0.25	85	3	100	16:1
4	1.1	0.5	85	4	90	8:1
5	2	0.5	85	1.25	100	13:1
6	3	0	85	3.5	24	50:1
7	1.5	1	20	18	44	1:1
8	1.5	0.5	20	18	25	0:1
9	1.5	0.5	85[b]	1.5	100	24:1

[a]Ratio determined from integration of crude ^{1}H NMR spectra. [b]The solution of alcohol was heated to 85 ºC prior to addition of salt **19** and imidazole.

Table 6 Optimisation of iodination reaction

When less than 1.5 equivalents of salt **327** was used the product ratio **324**:**325** was reduced and longer reaction times resulted (entry 4), whilst an increase in amount of salt **327** had no significant effect on either the ratio or reaction time (entry 5). Exclusion of imidazole, even with 3 equivalents of salt **327**, led to a high ratio of iodide **324**:formate **325**, but very slow reaction rate (entry 6). When the reaction was attempted at room temperature, the conversion was not only poor, but a significant increase in formate **325** formation was observed. In fact, when just 0.5 equivalents of imidazole was added, formate **325** was the sole product (entries 7 and 8).

For entries 1-6 (Table 6) the reagents were mixed together at room temperature and subsequently heated to 85 °C. In light of the observed formate formation at room temperature (entries 7 and 8), the reaction conditions of entry 2 was repeated but with alcohol **323** being heated to 85 °C in toluene prior to addition of salt **327** and imidazole (entry 9). Pleasingly, this almost doubled the ratio of iodide **324**:formate **325** to 24:1 and gave an isolated yield of 92% of iodide **324**. As a result of this optimisation study, it was decided that the conditions of entry 9 were the most effective and desirable for the iodination reaction in terms of reaction time, quantity of reagents needed and ratio of iodide **324**:formate **325** achieved.

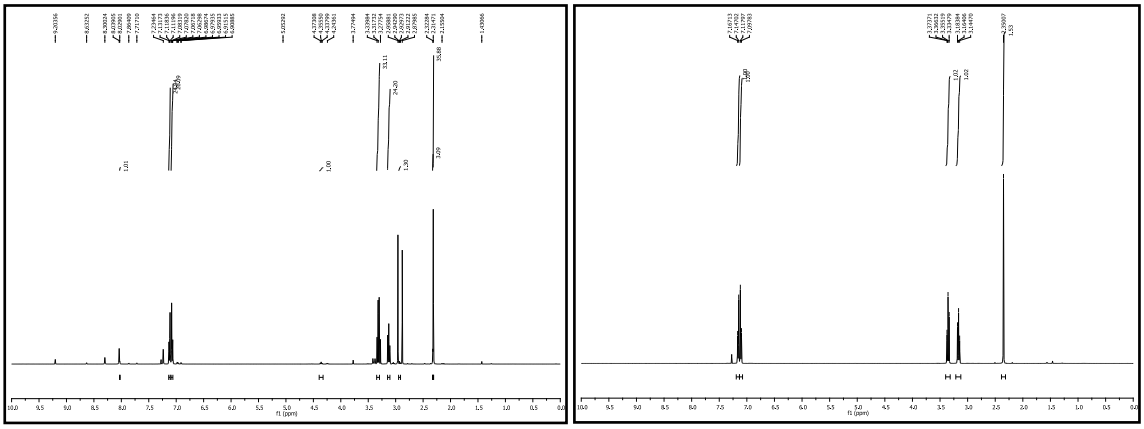


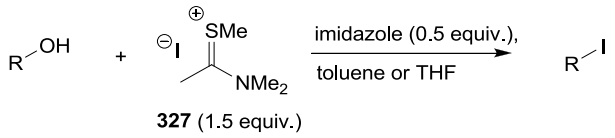
Figure 23 ^{1}H NMR spectra of crude (left) and purified (right) reaction products

A sample of salt **327** which had been stored at –25 °C for 18 weeks was used in the iodination reaction of alcohol **323** under the optimised conditions and gave iodide **324** in 90% yield. This small reduction in yield of only 2% meant that the salt could also be pre-formed and stored without any significant degradation well in advance of its use.

It is also noteworthy that the reaction requires no aqueous work-up; the reaction mixture is simply concentrated *in vacuo* to remove the solvent, methanethiol and most of the DMF to give the crude material with very few impurities present. Figure 23 shows the ^{1}H NMR spectra of crude and purified reaction products.

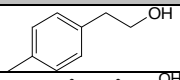
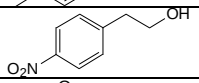
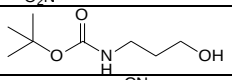
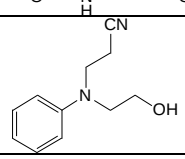
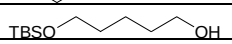
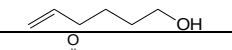
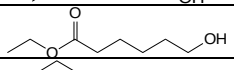
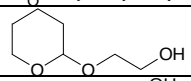
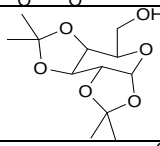
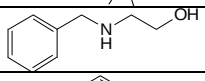
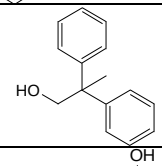
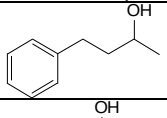
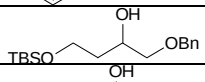
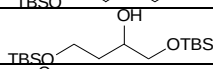
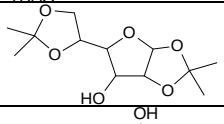
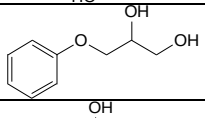
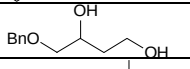
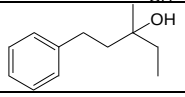
4.1.3.3 Scope

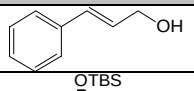
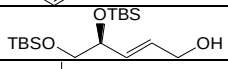
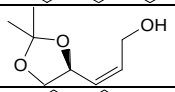
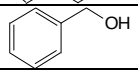
The scope and functional group compatibility of the iodination was next examined by treatment of various alcohols under the optimised conditions, in THF, toluene and acetonitrile. Despite early indications that acetonitrile was a suitable solvent (Table 5), it became evident at an early stage that this was not the case for all alcohol substrates; for example, the reaction in entry 3 (Scheme 90) did not work in acetonitrile, despite working well in THF and toluene. As a result, the scope of the iodination was investigated in THF and toluene only. Pleasingly, the iodination was found to be highly tolerant of a range of functional groups, including nitro, *tert*-butyl carbamate, tertiary amine, nitrile, silyl ether, alkene, ester and acetal moieties (entries 2-8). The yields obtained were generally excellent (82-93%) and reaction times were short. Additionally, a moderately hindered D-galactose derived primary alcohol (entry 9) was iodinated, albeit in slightly lower yield and longer reaction time.



327 (1.5 equiv.)

Scheme 90 Scope of iodination reaction

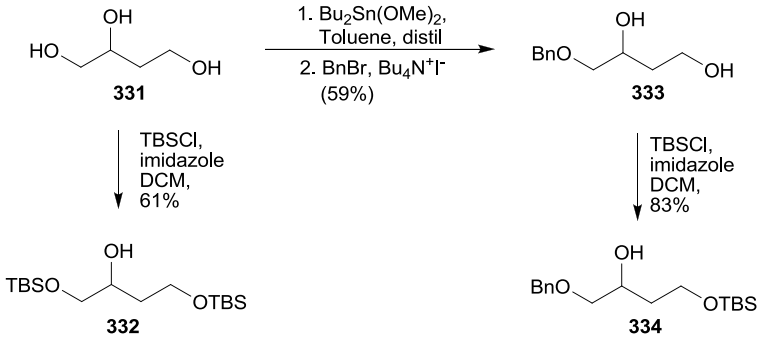
		Toluene			THF		
Entry	Alcohol	Time/h	Yield of iodide/%	Yield of formate/%	Time/h	Yield of iodide/%	Yield of formate/%
1		1.25	92	2	1	90[a,b]	4
2		1.5	84	3	1.5	85	4[c]
3		2	82	6	2	87[d]	4
4		1.33	91	3	1.5	87[e]	4
5		3.5	90	2	2.5	84	3
6		1.33	81	4	1	83	2
7		1.5	93	1	1.5	91	4
8		0.83	88	7	0.83	82	9
9		18	70	13	18	63	29
10		1.5	–	–	1.5	–	–
11[f]		2.5	0	27	2	0	24
12		3.5	86	3	2.5	87	3
13		48	75	6	48	70	8
14		72	60	0	48	76	0
15		6	0	10	7	0	16
16		3	62	2	2	59[g]	3[h]
17		1	82	8	1	83[g]	5[i]
18		6	–	–	6	–	–

		Toluene			THF		
Entry	Alcohol	Time/h	Yield of iodide/%	Yield of formate/%	Time/h	Yield of iodide/%	Yield of formate/%
19		5	–	–	5[j]	–	–
20		48	64	0	48[k]	61	0
21		2.5	71	0	4[k]	41	0
22		1	–	–	1[j]	–	–

[a] 90% yield obtained when reaction carried out using 18 week old salt **327** in toluene, taking 1.5 h. [b] In MeCN, 83% isolated yield . [c] Eliminated product also isolated in 7%/6% yield. [d] Reaction failed in MeCN. [e] In MeCN, 84% isolated yield. [f] Prepared directly from corresponding acid using $LiAlH_4$ in THF at room temperature for 1 h, in 79% yield. [g] Yield is of 1°-iodo-2°-alcohol compound. [h] Eliminated product **337** also isolated in 21% (Tol), 25% (THF). [i] Diiodide product also isolated in 3% (Tol), 3% (THF). [j] Reaction done at room temperature. [k] Reaction done at 55 ºC with a substrate concentration of 0.14 M.

Table 7 Iodination of a range of alcohols

Secondary alcohols can also be converted to iodides; in a slight modification to the general procedure, 1 equivalent of imidazole was required to accelerate the reaction and reaction times were extended in some cases (entries 12-14). The alcohols in entries 13, 14 and 17 (**334**, **332** and **333** respectively) were formed using standard procedures from triol **331** (Scheme 91).[111]



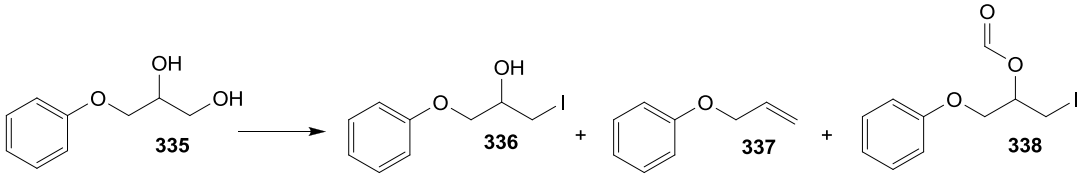
Scheme 91 Formation of alcohol precursors

Attempted iodination of allylic and benzylic alcohols proved troublesome due to their increased reactivity. For the reaction involving cinnamyl alcohol (entry 19), the starting material was consumed at room temperature; however no iodide was isolated. Similarly, no iodide product was seen for the reaction involving benzyl alcohol (entry 22). However, iodination of two allylic alcohols that are not additionally conjugated to

an aromatic ring (entries 20 and 21) was possible when the reaction was carried out under dilute conditions and at a reduced temperature.*

It was not possible to iodinate highly hindered alcohols such as the primary, secondary and tertiary alcohols of entries 11, 15 and 18. The increased steric encumbrance presumably prevents the iodide ion from being able to access the electrophilic carbon atom; for entries 11 and 15, a small amount of the corresponding formate was the only product isolated. In addition, secondary amine (entry 10) could not be iodinated and instead a complex mixture of products was isolated. Following this result, we believe that unprotected amines are incompatible functional groups to our reaction conditions as they are a competing nucleophile.

Given the observed difference in reaction rate between primary and secondary alcohols (entries 1-9 *vs* entries 12-14), we decided to a subject a primary-secondary diol to the iodination conditions to find out whether a selective reaction was possible. When 1,2-diol **335** was used (entry 16 and Scheme 92), the reaction gave rise to desired iodide **336** in mediocre yield; this is a consequence of the additional formation of dideoxygenated alkene side-product **337**. In addition, a small amount of formate **338** was isolated. In an attempt to thwart formation of alkene **337**, 1,3-diol **333** (entry 17) was tested. Diol **333** was prepared directly from 1,2,4-butanetriol (**331**, Scheme 91).



Scheme 92 Attempted iodination of a 1,2-diol

As expected, alcohol **333** was converted cleanly to primary iodide **339** in very good yield in both THF and toluene (entry 17 and Figure 24). This pleasing result indicates that selective iodination of primary alcohols in the presence of secondary alcohols is possible in good yield. In addition, benzyl ethers are yet another functional group compatible with the reaction conditions.

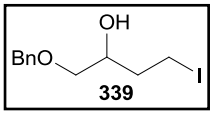
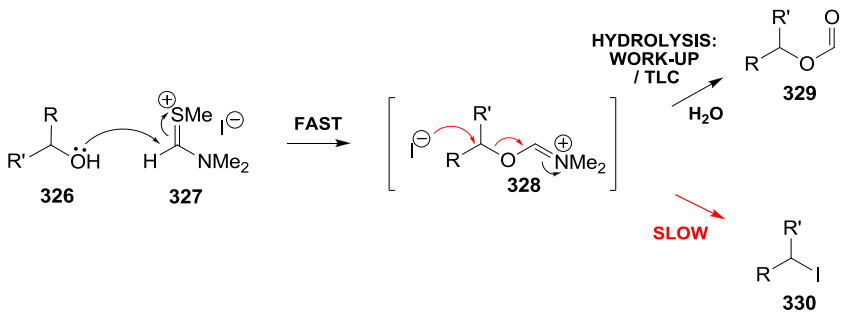


Figure 24

* Details regarding the formation of these alcohols can be found in section 2.

4.1.3.4 Origin of the formate by-product

Although in the early stages of this work it was unclear how the formate by-product was arising, the most likely reason for its formation was discovered whilst testing the scope of the reaction. It is now believed that formate by-product **329** is a consequence of hydrolysis of intermediate alkoxyiminium ion **328** *upon isolation*, rather than in the reaction mixture itself (Scheme 93). Hence, substrates that do not react further than the stable alkoxyiminium ion intermediate **328** would appear by TLC to have been converted into formate by-product **329** *in situ*, but in fact, this by-product was only a result of hydrolysis of alkoxyiminium ion **328** upon TLC.

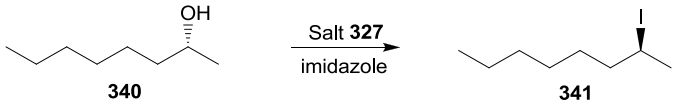


Scheme 93 Formation of formate by-product

This theory was reinforced on many occasions for a variety of alcohols, as the formation of the formate by-product was seen to decrease (when the reaction was monitored by ^{1}H NMR) as the reaction proceeded. We now believe that the second part of the reaction shown in Scheme 93 (i.e. the displacement of DMF by an iodide ion) proceeds *fastest* in toluene and THF, and hence during a set time period this results in a better conversion of the alkoxyiminium ion intermediate into the iodide product, giving less formate by-product.

4.1.3.5 Stereochemical course of the reaction

In order to determinine whether the iodination reaction proceeds via an S_N1 or S_N2 mechanism, the stereochemical course of the reaction was studied using (*R*)-octan-2-ol (**340**) as a substrate (Scheme 94). Samples were removed during the course of reactions and analysed by ^{1}H NMR and chiral GC (Figure 25).



Scheme 94 Conversion of (*R*)-octan-2-ol (**340**) to (*S*)-2-iodooctane (**341**)

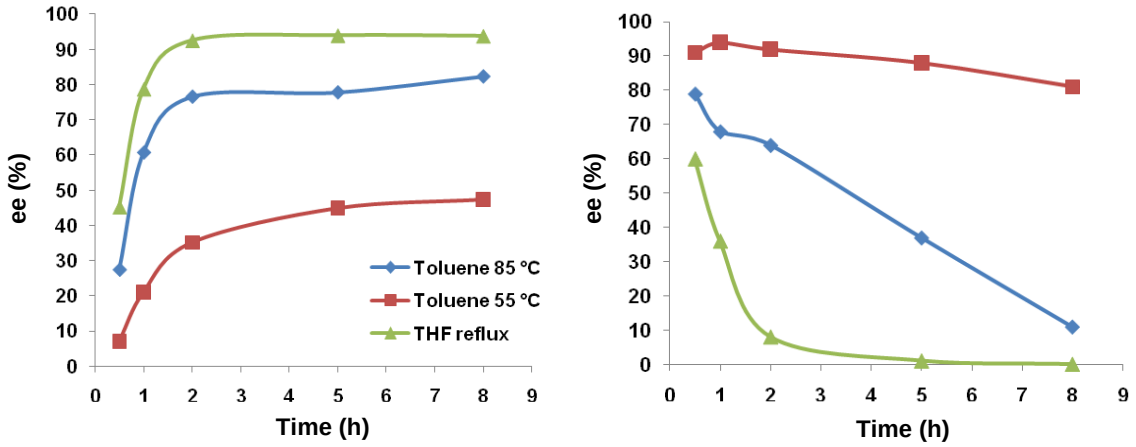


Figure 25 Percentage conversion to **341** (left) and enantiomeric excess of **341** in the reaction of alcohol **340** with salt **327** (right).

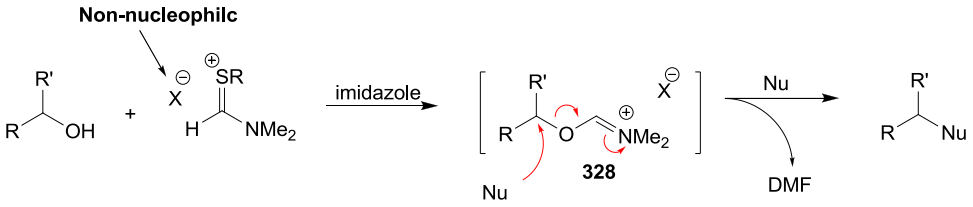
After 1 hour in toluene at 85 ºC, alcohol **340** had undergone 61% conversion to iodide **341**; the enantiomeric excess of this iodide was found to be 68%. As the reaction proceeded, the enantiomeric purity of the product dropped, and after 8 hours, the iodide could be isolated in 73% yield, but with only 11% ee. Similar results were obtained in THF at reflux, but with a more rapid formation of **341** and a more rapid deterioration of ee. After 8 hours, racemic **341** was obtained in 78% yield. Conversely, carrying out the reaction in toluene at 55 ºC led to slower conversion, but also to a slower degradation of the enantiomeric purity. In this case, the enantiomeric excess of iodide **341** after 8 hours was 81%.

These results suggest that the initial conversion of **340** to **341** occurs, as expected, with inversion of configuration; in the presence of excess iodide, however, further S_N2 reactions interconvert **341** and its enantiomer, racemising the product.[112]

4.2 C-X bond formation

We believed that it could be possible to use similar chemistry to that in the iodination procedure in order to form other types of bonds such as C-C, C-S and C-O. This could be achieved by performing the reaction using a thioiminium salt which has a non-

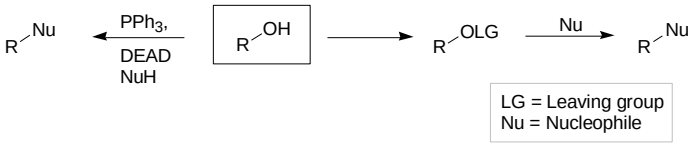
nucleophilic counterion (i.e. not an iodide ion) and then a nucleophile (Nu) of choice could be added (Scheme 95).



Scheme 95 Thioiminium salt with a non-nucleophilic counterion and its use to for other types of bonds

This type of reaction is appealing for a number of reasons: (i) the by-products are readily removable (as in the iodination procedure); (ii) the thioiminium salt should be easy to make; (iii) a C–OH bond would be converted into C–S, C–C or C–OR bond in a single step.

The two most common alternative ways to perform such a transformation are the Mitsunobu reaction or through the intermediacy of an activated substrate such as a halide or a sulfonate (Scheme 96).[113,114] The Mitsunobu reaction has the disadvantage of producing triphenylphosphine oxide as a by-product and the latter method is a two-step process.

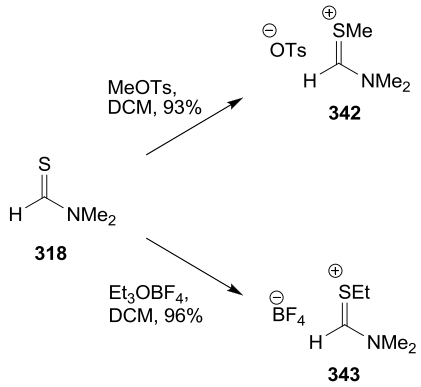


Scheme 96 Mitsunobu reaction (left) and two-step process (right)

4.2.1 Conversion of alcohols to 1-phenyltetrazol-5-yl sulfides[115]

4.2.1.1 Formation of thioiminium salts

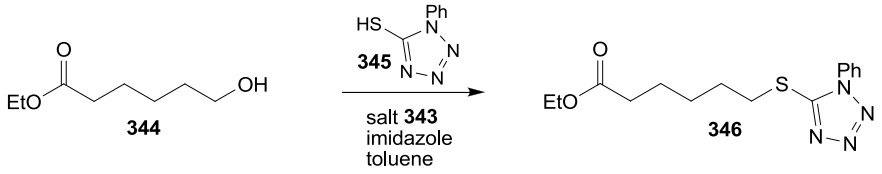
Initial studies in this area were carried out by an undergraduate student, Mark Frain. He initially targeted two thioiminium salts (**342** and **343**, Scheme 97), each of which was accessible from thioamide **318**; however, salt **343** was found to be a better choice as it was crystalline unlike salt **342**, and therefore easier to isolate and handle.



Scheme 97 Thioiminium salts with non-nucleophilic counterions

4.2.1.2 Formation of C-S bonds

Frain carried out initial studies with a range of nucleophiles, and 1-phenyl-(1*H*)-tetrazole-5-thiol (**345**) showed the most promise; this was appealing since use of a thiol nucleophile enables the formation of C-S bonds. In addition, we were aware that the products obtained from these transformations were desirable as they can be directly converted into Julia-Kocienski olefination precursors.[113,114]



Scheme 98 Attempted C-S bond formation using a thiol nucleophile

Following Frain's initial work, we set out optimise the reaction. Firstly, a solvent screen was implemented with various medium to high boiling point solvents; alcohol **344** was reacted with salt **343** (1.5 equivalents), imidazole (0.5 equivalents) and thiol **345** (1.2 equivalents). It was found that the reaction was slow in both THF and DMF (entries 2 and 4); however, the reaction was faster in MeCN (entry 3) and even more so in toluene (entry 1). As a result, toluene was the solvent of choice for this reaction (Table 8).

Entry[#]	Solvent	Temperature	Conversion to product / %
1	Toluene	90 ºC	91
2	THF	Reflux	52
3	MeCN	Reflux	83
4	DMF	90 ºC	57

[#]**Conditions**: 1.5 equiv. salt **343**, 0.5 equiv. imidazole, 1.2 equiv. thiol **345**, 18 h, 0.2M substrate conc.

Table 8 Solvent screen

Secondly, as the reaction took 18 hours for a 90% reaction conversion when salt **343** was used in toluene, salt **347** (made in 93% yield from thioamide **318** - Figure 26) was used in the reaction instead, with the hope that a faster rate would be observed. We considered that the rate might increase as methanethiol, as opposed to the less volatile ethanethiol, would be the by-product and hence any equilibrium between $ROCH(SR')NMe_2$ and $ROCH=N^+Me_2$ would be displaced to the right. However, this was not the case and the reaction rate did not increase. We therefore continued our studies with salt **343** as it is derived from cheaper starting materials.

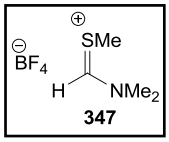
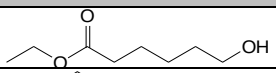
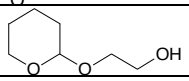
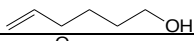
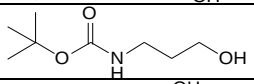
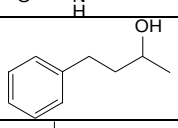
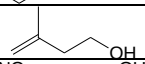
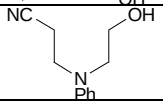
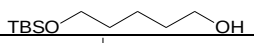
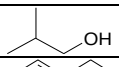
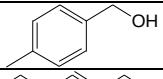
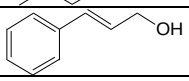


Figure 26

In an alternative attempt to increase the rate of reaction, we increased the concentration of the solution and the imidazole and thiol loading from 0.5 and 1.2 equivalents to 1 and 2 equivalents respectively; gratifyingly, the reaction went to completion in 18 h and the ^{1}H NMR spectrum of the crude reaction mixture showed fewer impurities in the crude material. Using these new conditions, the yield of the sulfide product obtained with alcohol **344** as the starting material was 76% (entry 1, Table 9).

Entry[a]	Alcohol	Time / h	Isolated yield of sulfide / %
1		18	76
2[b]		18	80
3		18	70
4[b]		24	76
5		18	83
6		18	67
7[c]		18	88
8[b]		18	62[d]
9		6	75
10[e]		1	91
11[e]		1	90

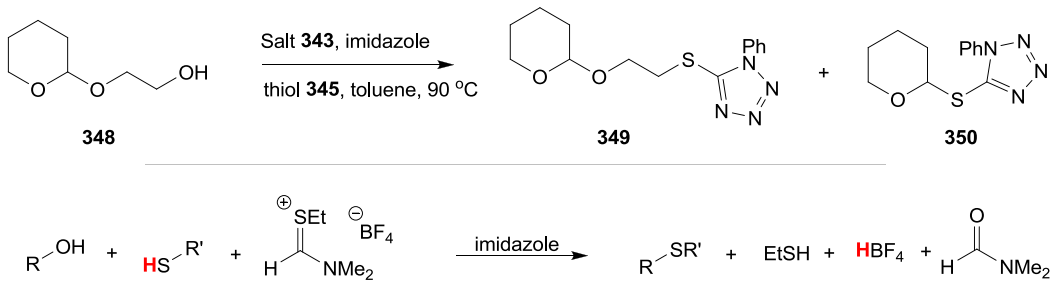
[a] **General reaction conditions**: 1.5 equiv. salt **343**, 1 equiv. imidazole, 2 equiv. thiol **345**, toluene (substrate conc. 0.4-0.5 M), 90 ºC. [b] Acid sensitive: 5 equiv. Imidazole required. [c] 2 equiv. imidazole added. [d] Yield is of deprotected product, i.e. ε-hydroxy sulfide. [e] Allylic or benzylic: 1.2 equiv. thiol.

Table 9 Scope of sulfide formation reaction

The scope of the optimised procedure was then examined and the results can be seen in Table 9. For substrates that do not possess acid sensitive functional and/or protective groups (entries 1, 3, 5, 6, 7, 9, 10 and 11), the corresponding sulfide products could be obtained in good yield; the reaction works with primary (linear and branched), secondary, allylic and benzylic alcohols, requires no aqueous work-up and functional groups such as esters, nitriles, alkenes and tertiary amines are compatible. For benzylic and allylic alcohols, the thiol loading was reduced to 1.2 equivalents and the reaction time was significantly less due to the increased rate of reaction.

However, for acid sensitive substrate **348** (a THP ether), under the same conditions, the desired product was only isolated in 31% yield as it was accompanied by a significant amount of by-product **350** in 32% yield; we believe that this product is formed after initial deprotection of the alcohol by an acid source, followed by attack onto the oxonium ion by thiol **345** (Scheme 99, top).

The lack of stability of this acid sensitive group to our reaction conditions was thought to be a consequence of the formation of HBF_4 (Scheme 99, bottom).



Scheme 99 Formation of by-product **350** (top) and generation of HBF_4 during the reaction (bottom)

To overcome this problem, we first tried the reaction involving alcohol **348** using the sodium salt of thiol **345** instead of thiol **345** itself (so that $NaBF_4$ rather than HBF_4 would be the by-product). However, the lack of solubility of the thiolate anion in the solvent resulted in a very slow reaction and 100% conversion to the product was not possible. We next reverted to thiol **345** as the nucleophile and varied the amount of imidazole added; it was believed that extra imidazole would buffer the acid formed and therefore make the conditions more suitable for acid sensitive substrates (Table 10).

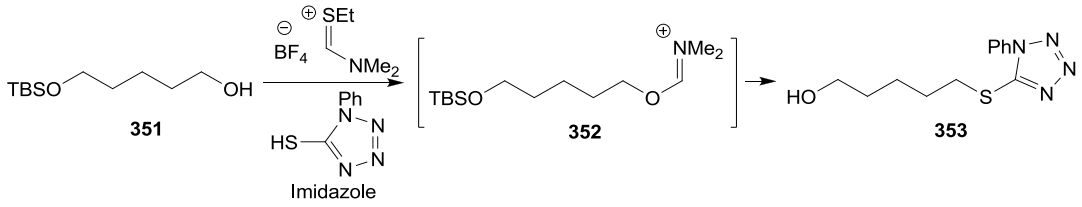
Entry	Equivalents of imidazole	Ratio of products **349**:**350**	Yield **349** / %	Yield **350** / %
1	0.5	1:5.4	–	–
2	1	1:1.4	31	32
3	2	1:0.4	–	–
4	5	1:0	80	0

*__Conditions__: 1.5 equiv. salt **343**, imidazole (above), 2 equiv. thiol **345**, toluene, 90 ºC, 18 h, 0.4-0.5 M substrate concentration

Table 10 Optimisation of imidazole loading for acid sensitive substrates

It was found that on increasing the imidazole loading to 2 equivalents, the amount of by-product **350** obtained decreased; with 5 equivalents of imidazole used (entry 4), no by-product **350** was present and sulfide **349** was isolated in 80% yield.

We next tested the newly optimised conditions (i.e. 5 equivalents of imidazole for acid sensitive substrates) on two other acid sensitive alcohols - a Boc-protected amine (entry 4, Table 9) and silyl ether respectively (entry 8, Table 9). For the reaction involving the Boc-protected amine a 76% yield was obtained and no by-products were evident in the ^{1}H NMR spectrum of the crude reaction mixture. However, when silyl-protected alcohol **351** (entry 8) was used in the reaction, alcohol **353** was isolated as the sole product in 62% yield (Scheme 100). We believe that the BF_4^- counterion may supply the fluoride ion that attacks the silicon atom and leads to deprotection.



Scheme 100 Deprotection of silyl ether in C-S bond forming step

4.2.1.3 Attempted conversion of alcohols to phenyl sulfides

Thiophenol was briefly examined examined in place of thiol **345** in the reaction with alcohol **351**. Interestingly, when thiophenol (**355**) was used, no sulfide product was obtained; instead, the corresponding formate (which is formed upon hydrolysis of alkoxyiminium ion intermediate **328**, Scheme 95) was isolated as the sole product.

The lack of reactivity of thiophenol suggests that the high acidity of thiol **345** (pK_a = 2.9[116] *vs*. 6.5 for thiophenol [116]) may be an important factor in the observed success of this reaction. The low pK_a of thiol **345** means that it will be largely deprotonated by the imidazole present in solution (pK_{BH+} = 7.0); as a result, it may be thiol anion **354** that is reacting. Conversely, thiophenol cannot be deprotonated to anion **356** as easily and therefore reacts slowly due to its lower nucleophilicity (Figure 27).

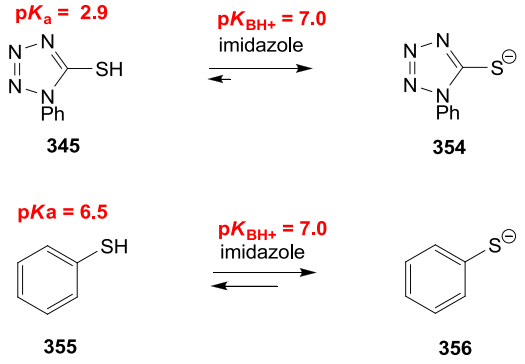
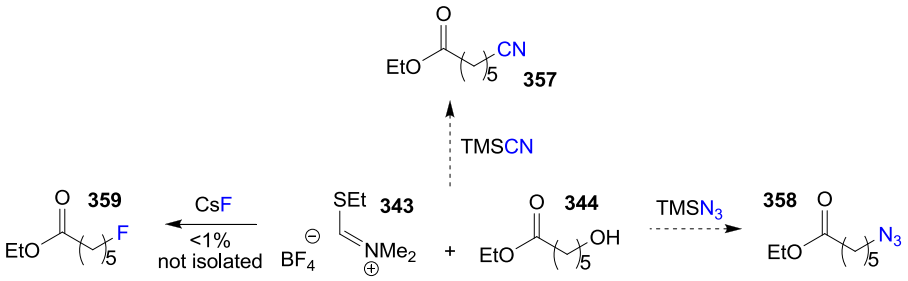


Figure 27 Thiol nucleophiles and their corresponding anions

4.2.1.4 Attempted conversion of alcohols to fluorides, azides and nitriles

The results obtained from our attempts to form other types of bonds can be seen in Scheme 101.



Scheme 101 Attempted formation of nitriles, azides and fluorides

We were unable to synthesise nitrile **357** using TMSCN as the nucleophile or azide **358** using $TMSN_3$ as the nucleophile; all that could be isolated from these reactions was the corresponding formate and silylated alcohol products. In order to produce more active nucleophiles, methanol (1 equivalent) was also added to both reactions (it was hoped that MeOTMS would form and therefore release the more nucleophilic anions CN^- or N_3^-); however this did not result in an improved reaction.

Formation of C-F bonds was also attempted and we were encouraged when a small amount of fluoride **359** was seen in the crude ^{1}H NMR spectrum from the reaction involving CsF as a nucleophile (Scheme 101);* however, despite several alterations to the conditions so that the nucleophilicity of the fluoride source would increased (Table 11), we were unable to improve this result and were not able to isolate fluoride **359**.

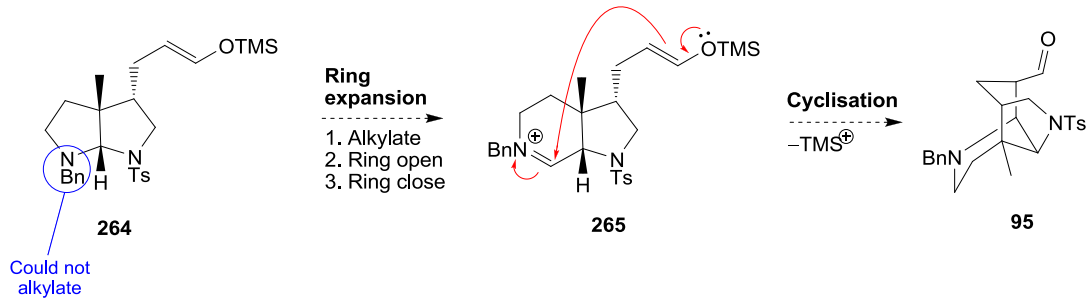
Nucleophile conditions	Result
CsF	<1% in crude
KF or NaF	No product
KF/18-crown-6	No product
(^{t}BuOH)$_4$TBAF[117]	No product

Table 11 Fluoride formation conditions

* The fluoride was identified by observation of a CH_2F group ($^{2}J_{HF}$ = 47.3 Hz) at 4.4 ppm, and by comparison with literature data for this compound.[118]

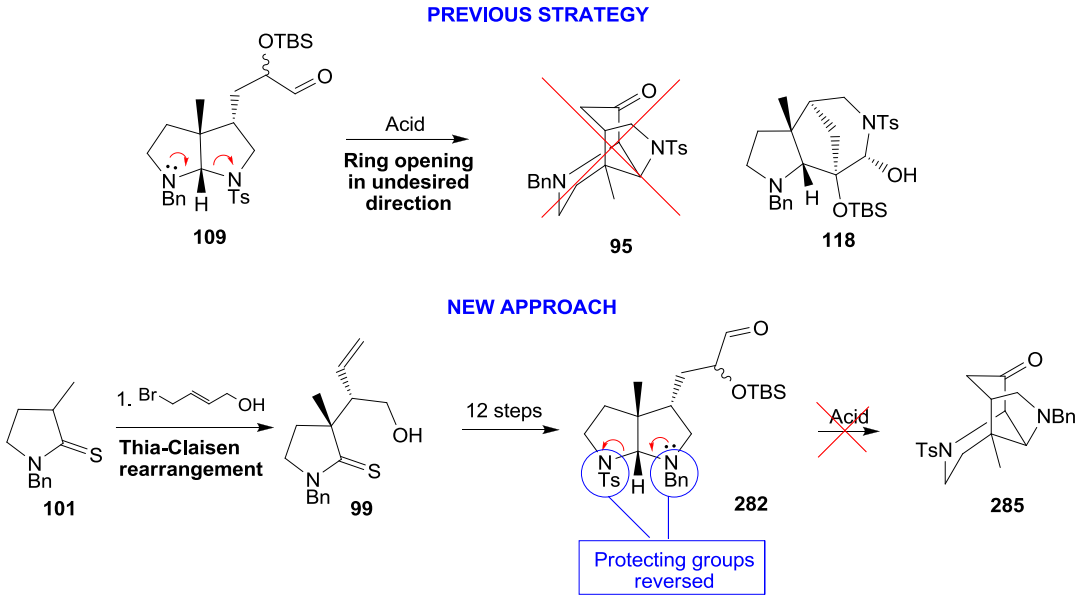
5 Conclusions and future perspectives

This thesis has described two distinct approaches that have been taken in order to synthesise the sarain core. The first strategy towards the sarain core involved a ring expansion of bicycle **264** to give iminium ion **265**, which would subsequently cyclise to give tricyclic core **95** (Scheme 102). However, due to the inherent lack of nucleophilicity of the benzyl protected nitrogen atom in a model system, the initial alkylation step could not be achieved despite many attempts.



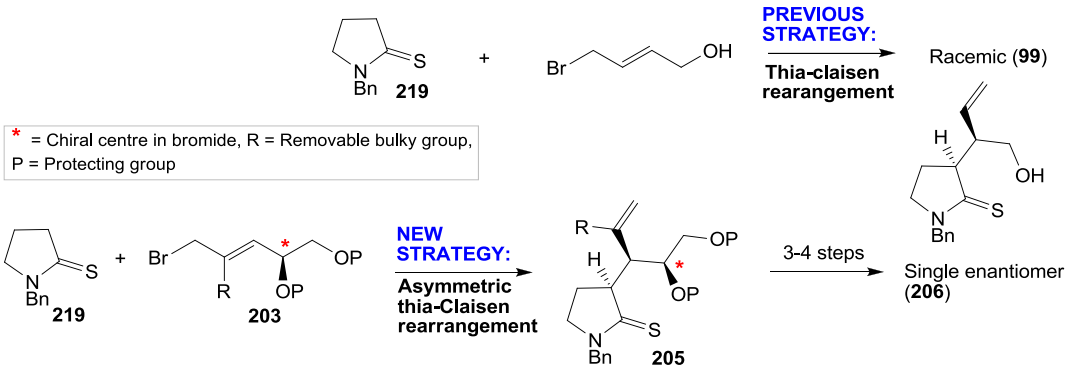
Scheme 102 Attempted ring expansion approach towards the core of sarains A-C

The second approach towards the sarain core involved the modification of an acid catalysed ring opening strategy that had previously been developed within the group (Scheme 103). In this approach, to prevent the bicycle from opening in the undesired direction during the key ring opening step (as had occurred previously within the group's studies), the protecting groups on the two nitrogen atoms were exchanged. The precursor for this rearrangement was therefore made in 13 steps from thiolactam **101**; synthesis of bicycle **282** was not as straightforward as first envisaged due to the increased electron withdrawing nature of the sulfonamide motif compared to the benzyl protecting group. The key rearrangement step was attempted only once, on a small scale, due to time constraints; unfortunately, examination of the crude ^{1}H NMR spectrum from this reaction showed no signs of the formation of core structure **285**. Future work with regards to this strategy would involve re-attempting the key cyclisation step under different acidic conditions.



Scheme 103 Previous and revised approach towards the core

A vital step in all of our current and previous attempted syntheses of the sarain core is a thia-Claisen rearrangement that provides key intermediate **99** (Scheme 103) as a racemic product with the correct relative stereochemistry; this thesis also provides information on an asymmetric variant of this rearrangement that has been developed (Scheme 104).

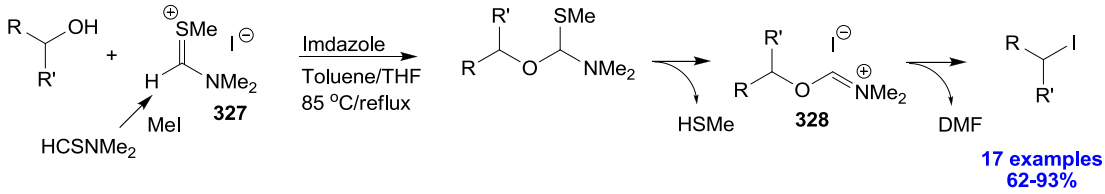


Scheme 104 Past and present thia-Claisen rearrangements: racemic and asymmetric

It was found that introduction of a fixed chiral centre into the bromide precursor for this rearrangement (in the form of an acetonide motif or a di-silyl ether) was effective in providing moderate to excellent diastereoselectivity in the thia-Claisen rearrangements (2.5:1 to 30:1). Additionally, in an attempt to increase allylic strain and therefore enhance the level of diastereoselectivity achieved, a bulky removable group (a bromine atom) was placed onto the double bond of bromide precursor **203**; surprisingly, upon

thia-Claisen rearrangement, the diastereomeric ratio increased and *reversed* from 2.5:1 to 1:12. All of the bromides used in the [3,3]-sigmatropic rearrangements were made from commercial D-mannitol. Future work in this area may involve investigating a series of Claisen-like rearrangements of precursors that contain a bromine atom on the double bond, to see whether the increase and reversal in diastereoselectivity that was seen in our thia-Claisen rearrangement occurs for the [3,3]-sigmatropic rearrangements of other substrates.

Whilst working towards the core of sarain A, previous members of the group had discovered that a small amount of iodide **317** is generated upon reaction of thiolactam **99** with methyl iodide and mild aqueous base; after removal of all water from this reaction, we have since found that iodide **317** can be isolated as the sole product (Scheme 81 and Scheme 82). The chemistry discovered in this unexpected intramolecular alcohol iodination was then used to enable the development of a new *inter*molecular alcohol iodination reaction (Scheme 105)

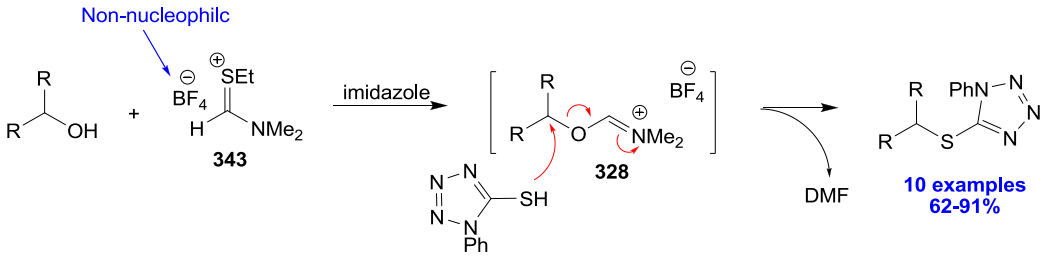


Scheme 105 Novel alcohol iodination method using a thioiminium salt

In this novel iodination reaction, a primary, secondary or allylic alcohol is reacted with thioiminium salt **327** and imidazole to form alkoxyiminium ion **328**; subsequent attack from the iodide nucleophile gives rise to the corresponding iodide. The reaction is high yielding, tolerant of a wide variety of functional and protecting groups and the thioiminium salt is stable for several months. In addition, purification is very straightforward; the crude material is simply concentrated *in vacuo* to remove the volatile DMF and methanethiol by-products. The major advantage of this procedure over existing phosphorus based methods is that no triphenylphosphine oxide is produced as a by-product, which can cause problems during product purification.

The aforementioned methodology was then extended to allow the formation of other types of bonds, namely sulfides. In this approach (Scheme 106), the alcohol is mixed with salt **343**, (which has a non-nucleophilic counterion) along with imidazole to form

alkoxyiminium ion intermediate **328** in a similar fashion to that shown in Scheme 105; the thiol nucleophile then attacks this intermediate to give rise to the corresponding sulfide.



Scheme 106 Novel alcohol to sulfide reaction

As is the case for the iodination procedure (Scheme 105), products can be purified using this method very easily in good yields. The thioiminium salt is also stable and many of the common functional and protecting groups are tolerated. In comparison to the iodination procedure, reaction times are generally longer, however, formation of allylic and benzylic sulfides could be achieved in higher yields in shorter reaction times.

6 Experimental

General

All reactions that that were performed in non-aqueous conditions were carried out under an argon atmosphere in a flame dried flask.

Chemicals

Chemicals were purchased from Alfa Aesar, Acros, Avocado, Fisher, Fluka, Lancaster and Sigma-Aldrich Co. Ltd and were used without any further purification, unless stated otherwise.

- NEt_3 was distilled from CaH_2 and stored over KOH.
- Pyridine was distilled from CaH_2 and stored over 4 Å molecular sieves.
- NBS and TsCl were recrystallised according to the procedure given in *Purification of Laboratory Materials*.[119]
- Lawesson's Reagent was prepared using the procedure by Clausen *et al*.[120]
- DMP was prepared using the procedure by Boeckman *et al*.[121]

Solvents

Anhydrous DCM, THF, toluene, hexane, MeCN and ether were obtained after passing through alumina drying columns (UCL Anhydrous Solvent System) and were stored under argon over anhydrous molecular sieves.

- DMF was distilled from, and stored over 4 Å molecular sieves
- DMSO was distilled from CaH_2 and stored over 4 Å molecular sieves

Petrol refers to petroleum ether, boiling point = 40-60 ºC.

Chromatography

Flash chromatography was carried out on Merck silica gel 60 (40-60 μm) or either neutral or slightly acidic aluminium oxide (deactivated to grade III with 6% w/v water, 50-200 μm).

Preparative TLC was performed on a glass plate pre-coated with normal phase Merck silica gel 60 F_{254}, 0.25 mm thickness.

TLC was performed on Merck Kieselgel 60 F_{254} aluminium sheets, visualised at short wavelength ultraviolet light (254 nm) and was stained with either potassium permanganate, iodine, CAM, 2,4-dinitrophenylhydrazine or vanillin.

Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-300, Bruker AVANCE-400, Bruker AVANCE-500 and Bruker AVANCE-600 spectrometers. ^{1}H and ^{13}C NMR shifts are given in parts per million (ppm), and are quoted with reference to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.26 ppm, C_6HD_5 in C_6D_6 at 7.16 ppm, CHD_2OD in CD_3OD at 3.31 ppm for ^{1}H NMR and 77.0 ppm, 128.1 ppm, 49.0 ppm for ^{13}C NMR respectively). The signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet (and combinations thereof), quin = quintet, non = nonet, m = multiplet, br = broad. Coupling constants, *J*, are given in hertz. COSY, HSQC, HMBC and DEPT were used to aid all assignments of spectra.

IR were recorded on a PerkinElmer Spectrum 100 FTIR (ATR mode). Signals are denoted as br = broad. Mass spectra were recorded using a VG ZAB-SE or ZAB-SE4F instrument by Dr Lisa Harris (UCL).

Miscellaneous

Melting points were determined with an Electrothermal 9100 instrument.

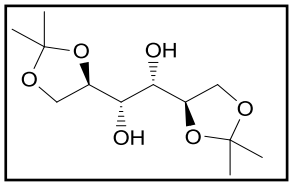
Optical rotations ($[\alpha]_D$) were recorded with a Perkin Elmer 343 polarimeter.

Chiral GC analysis was carried out using a Supelco Beta-Dex™ 120 column (30 m × 0.25 mm i.d.); carrier gas He, flow rate 100 mL min^{-1}, oven temperature 80 ºC (20 min) then increasing at 2 ºC per min.

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 681439. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1 EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http:// www.ccdc.ac.uk.

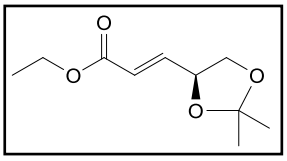
ASYMMETRIC THIA-CLAISEN REARRANGEMENT

1,2:5,6-Di-*O*-isopropylidene-D-mannitol (210)[68,69]



A solution of D-mannitol (**209**, 10.0 g, 54.9 mmol), *para*-toluenesulfonic acid (52.0 mg, 0.30 mmol) and 2,2-dimethoxypropane (14.3 g, 137 mmol) in DMSO (20 mL) was stirred at rt for 24 h. To this solution was added 3% aq. $NaHCO_3$ (100 mL) and the organic material extracted with EtOAc (3 × 100 mL), washed with H_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The solid was recrystallised from hexane/EtOAc, washed with cold Et_2O/hexane (1:3) and dried to give diol **210** (6.19 g, 43%) as a white solid: mpt. 122-123 °C [lit.[122] = 118-120 °C]; $[\alpha]_D^{17}$ +2.1 (*c* 0.80 in $CHCl_3$) [lit.[123] +6.0 (*c* 0.60 in $CHCl_3$)]; υ_{max}/cm^{-1} (KBr disc) 3315br, 2982, 1068; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (6H, s) and 1.42 (6H, s, 2 × C(C**H**$_3$)$_2$), 2.56 (2H, br s, O**H**), 3.74 (2H, d, *J* 6.3 Hz, C**H**OH), 3.98 (2H, dd, *J* 8.4, 5.4 Hz, OC**H**H), 4.03-4.22 (4H, m, OCH**H** and CH_2C**H**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.2 and 26.7 (2 × C(**C**H$_3$)$_2$), 66.7 (**C**H$_2$), 71.2 (**C**HOH). 76.2 (CH_2**C**H), 109.4 (**C**Me$_2$); *m*/*z* (ESI) 285 (MNa^+, 100%), 263 (9). HRMS found 285.1321, $C_{12}H_{22}O_6Na$ (MNa^+) requires 285.1309.

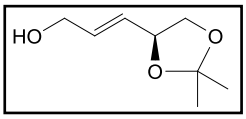
(*S*,*E*)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (213)[68]



To a solution of diol **210** (5.99 g, 22.8 mmol) in aq. $NaHCO_3$ (5% w/v, 50 mL) at 0 °C was added a solution of $NaIO_4$ (6.00 g, 27.6 mmol) in H_2O (50 mL) and the resulting solution stirred for 1 h. After cooling the mixture to 0 °C, triethyl phosphonoacetate (19.0 mL, 95.1 mmol) and K_2CO_3 (6 M, 150 mL) were added successively, whilst the temperature was maintained at 0 °C. After stirring the solution at rt for 24 h, H_2O was added to dissolve the solid present, and the organic material was extracted with DCM (4 × 120 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1) afforded ester **213** (7.84 g, 86%) as a colourless oil: $[\alpha]_D^{19}$ +32.8 (*c* 0.74 in $CHCl_3$) [lit.[124] +38.0 (*c* 1.00, $CHCl_3$)]; υ_{max}/cm^{-1} (thin film) 2986, 1720, 1651; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (3H, t, *J* 7.2 Hz, C**H**$_3$CH$_2$), 1.40 (3H, s) and 1.45

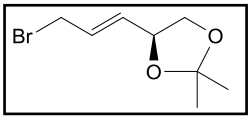
(3H, s, C(C**H**$_3$)$_2$), 3.67 (1H, dd, *J* 8.2, 7.1 Hz, C**H**HCH), 4.08-4.24 (3H, m, CH**H**CH and C**H**$_2$CH$_3$), 4.66 (1H, td, *J* 7.1, 5.6 Hz, OC**H**), 6.09 (1H, dd, *J* 15.6, 1.4 Hz, O=CC**H**), 6.87 (1H, dd, *J* 15.6, 5.6 Hz, O=CCH=C**H**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (**C**H$_3$CH$_2$), 25.7 and 26.4 (C(**C**H$_3$)$_2$), 60.6 (CH$_3$**C**H$_2$), 68.8 (**C**H$_2$CH), 74.9 (CH$_2$**C**H), 110.2 (**C**Me$_2$), 122.4 (O=CCH=**C**H), 144.6 (O=C**C**H), 166.0 (O=**C**) ; *m*/*z* (FAB$^+$) 201 (MH$^+$, 76%), 185 (29), 154 (100); HRMS found 201.1120, $C_{10}H_{17}O_4$ (MH$^+$) requires 201.1127.

(*S*,*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (214)[70]



To a solution of ester **213** (6.05 g, 30.2 mmol) in DCM (90 mL) at –78 °C was added DIBAL (1.2 M in toluene, 62.9 mL, 75.5 mmol) dropwise, and the resulting mixture stirred for 3 h at –78 °C. After warming to rt, MeOH (150 mL), Et$_2$O (200 mL) and aq. sat. Rochelle's salt (200 mL) were added successively, and the solution stirred for 1 h. The aqueous phase was diluted with H$_2$O (120 mL) and the organic material was extracted with EtOAc (4 × 150 mL), washed with brine (150 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO$_2$, petrol/EtOAc 7:3) provided alcohol **214** (4.14 g, 87%) as a pale yellow oil: $[\alpha]_D^{19}$ +33.3 (*c* 1.00 in $CHCl_3$) [lit.[125] +33.9 (*c* 3.60 in $CHCl_3$)]; υ_{max}/cm^{-1} (thin film) 3395br (OH), 2986 (CH), 1680 (C=C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (3H, s) and 1.43 (3H, s, C(C**H**$_3$)$_2$), 3.60 (1H, t, *J* 7.9 Hz, CH=CHCHC**H**H), 4.11 (1H, dd, *J* 8.2, 6.2 Hz, CH=CHCHCH**H**), 4.18 (2H, dd, *J* 5.1, 1.4 Hz, C**H**$_2$OH), 4.53 (1H, m, CH=CHC**H**), 5.72 (1H, dd, *J* 15.5, 7.5 Hz, HOCH$_2$CH=C**H**), 5.96 (1H, dt, *J* 15.5, 5.1 Hz, HOCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9 and 26.7 (C(**C**H$_3$)$_2$), 62.5 (**C**H$_2$OH), 69.3 (CH=CHCH**C**H$_2$), 76.5 (CH=CH**C**HCH$_2$), 109.4 (**C**Me$_2$), 128.3 (HOCH$_2$CH=**C**H), 133.6 (HOCH$_2$**C**H=CH).

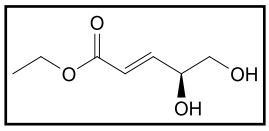
(*S*,*E*)-4-(3-Bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (207)[70]



To a stirred solution of alcohol **214** (0.75 g, 4.74 mmol) in DCM (50 mL) at 0 °C was added triphenylphosphine (1.37 g, 5.22 mmol), followed by NBS (0.89 g, 5.00 mmol) portionwise over a few minutes. The solution was stirred at rt for 2 h and then the reaction was quenched with H$_2$O (30 mL).

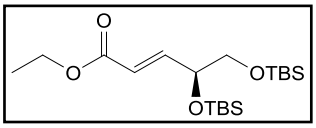
The organic material was then extracted with DCM (3 × 90 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 4:1) afforded bromide **207** (0.96 g, 93%) as a colourless oil: $[\alpha]_D^{19}$ +50.0 (*c* 1.02 in $CHCl_3$); υ_{max}/cm^{-1} (thin film) 2986; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (3H, s) and 1.42 (3H, s, C(C**H**$_3$)$_2$), 3.61 (1H, t, *J* 7.6 Hz, OC**H**H), 3.92 (2H, d, *J* 7.4 Hz, C**H**$_2$Br), 4.10 (1H, dd, *J* 8.2, 6.3 Hz, OCH**H**), 4.52 (1H, m, OC**H**), 5.75 (1H, dd, *J* 15.2, 7.1 Hz, BrCH$_2$CH=C**H**), 6.00 (1H, dt, *J* 15.2, 7.6 Hz, BrCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8 and 26.6 (C(**C**H$_3$)$_2$), 31.3 (**C**H$_2$Br), 69.2 (O**C**H$_2$), 75.8 (O**C**H), 109.6 (**C**Me$_2$), 129.7 (BrCH$_2$CH=**C**H), 132.5 (BrCH$_2$**C**H=CH).

(*S*,*E*)-Ethyl 4,5-dihydroxypent-2-enoate (215)



A solution of ester **213** (1.00 g, 5.00 mmol) in aq. AcOH (60% v/v, 50 mL) was stirred at rt for 24 h. Petrol (50 mL) was added and the aq. layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 50 mL) and toluene (3 × 50 mL) to give diol **215** (0.78 g, 98%) as a cloudy oil: $[\alpha]_D^{20}$ –8.0 (*c* 1.03 in $CHCl_3$) [lit.[64] –5.5 (*c* 1.57 in $CHCl_3$)]; υ_{max}/cm^{-1} (thin film) 3398br, 2937, 1715, 1659; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (3H, t, *J* 7.2 Hz, C**H**$_3$), 2.34-2.89 (2H, br s, O**H**), 3.55 (1H, dd, *J* 11.2, 6.9 Hz, C**H**HOH), 3.77 (1H, dd, *J* 11.2, 3.2 Hz, CH**H**OH), 4.22 (2H, q, *J* 7.2 Hz, CH$_3$C**H**$_2$), 4.43 (1H, br s, C**H**OH), 6.14 (1H, dd, *J* 15.7, 1.7 Hz, O=CC**H**=CH), 6.90 (1H, dd, *J* 15.7, 4.4 Hz, O=CCH=C**H**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (**C**H$_3$), 60.7 (CH$_3$**C**H$_2$), 65.5 (**C**H$_2$OH), 71.7 (**C**HOH), 122.0 (O=C**C**H=CH), 146.2 (O=CCH=**C**H), 166.6 (**C**=O); *m*/*z* (CI) 161 (MH$^+$, 51%), 143 (55), 115 (52) 97 (100); HRMS found 161.0803, $C_7H_{13}O_4$ (MH$^+$) requires 161.0808.

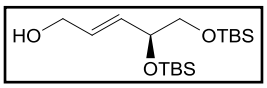
(*S*,*E*)-Ethyl 4,5-bis(*tert*-butyldimethylsilyloxy)pent-2-enoate (216)



To a solution of diol **215** (5.00 g, 31.2 mmol) and imidazole (8.50 g, 125 mmol) in DCM (80 mL) at 0 °C was added TBSCl (10.4 g, 68.7 mmol) and the mixture stirred at rt for 4 h. The solution was diluted with H_2O (250 mL), the organic material extracted with DCM (3 × 150 mL), washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by

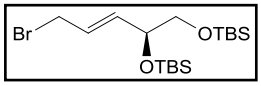
flash chromatography (SiO_2, petrol/EtOAc 49:1) afforded ester **216** (9.35 g, 77%) as a colourless oil: $[\alpha]_D^{19}$ –25.2 (*c* 0.68 in $CHCl_3$); υ_{max}/cm^{-1} (thin film) 2930, 1725, 1661; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01-0.07 (12H, m, 2 × Si(C**H**$_3$)$_2$), 0.87 (9H, s) and 0.89 (9H, s, 2 × C(C**H**$_3$)$_3$), 1.27 (3H, t, *J* 7.1 Hz, C**H**$_3$CH$_2$), 3.48 (1H, dd, *J* 9.9, 6.5 Hz, TBSOC**H**H), 3.58 (1H, dd, *J* 9.9, 6.3 Hz, TBSOCH**H**), 4.19 (2H, q, *J* 7.1 Hz, CH$_3$C**H**$_2$), 4.30-4.35 (1H, m, TBSOC**H**), 6.04 (1H, dd, *J* 15.6, 1.8 Hz, O=CC**H**=CH), 7.01 (1H, dd, *J* 15.6, 4.2 Hz, O=CCH=C**H**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.8 and –4.8 (2 × Si**C**H$_3$), 14.3 (**C**H$_3$CH$_2$), 18.3 and 18.4 (2 × **C**Me$_3$), 25.8 and 25.9 (2 × C(**C**H$_3$)$_3$), 60.3 (CH$_3$**C**H$_2$), 67.2 (TBSO**C**H$_2$), 72.7 (TBSO**C**H), 120.8 (C=O**C**H=CH), 148.6 (C=OCH=**C**H), 166.8 (O=**C**); *m*/*z* (ES^+) 411 (100), 389 (MH^+, 50%), 257 (64); HRMS found 389.2556, $C_{19}H_{41}O_4Si_2$ (MH^+) requires 389.2538.

(*S*,*E*)-4,5-Bis(*tert*-butyldimethylsilyloxy)pent-2-en-1-ol (217)



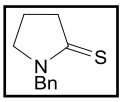
To a solution of ester **216** (4.00 g, 10.3 mmol) in DCM (35 mL) at –78 °C was added DIBAL (1.2 M in toluene, 20.7 mL, 24.7 mmol) dropwise, and the resulting mixture stirred for 4 h at –78 °C. After warming the reaction mixture to rt, MeOH (50 mL), Et_2O (60 mL) and aq. sat. Rochelle's salt (50 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (50 mL), organic material extracted with EtOAc (3 × 50 mL), washed with brine (30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1) provided alcohol **217** (3.05 g, 85%) as a colourless oil: $[\alpha]_D^{19}$ –16.8 (*c* 0.63 in $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3332br, 2929; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03-0.07 (12H, m, 2 × Si(C**H**$_3$)$_2$), 0.88 (9H, s) and 0.89 (9H, s, 2 × C(C**H**$_3$)$_3$), 1.41 (1H, br s, O**H**), 3.44 (1H, dd, *J* 10.0, 5.9 Hz, TBSOC**H**H), 3.53 (1H, dd, *J* 10.0, 6.5 Hz, TBSOCH**H**), 4.14-4.21 (3H, m, TBSOC**H** and C**H**$_2$OH**)**, 5.72 (1H, dd, *J* 15.5, 3.8 Hz, HOCH$_2$CH=C**H**) 5.87 (1H, dt, *J* 15.5, 5.2 Hz, HOCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.6 (Si(**C**H$_3$)$_2$), 18.3 and 18.4 (2 × **C**Me$_3$), 25.9 and 26.0 (2 × C(**C**H$_3$)$_3$), 63.3 (**C**H$_2$OH), 68.0 (TBSO**C**H$_2$), 73.5 (TBSO**C**H), 129.6 (HOCH$_2$**C**H=CH), 132.3 (HOCH$_2$CH=**C**H); *m*/*z* (ES^+) 369 (MNa^+, 100%), 215 (17); HRMS found 369.2268, $C_{17}H_{38}O_3Si_2Na$ (MNa^+) requires 369.2252.

(*S*,*E*)-1-Bromo-4,5-bis(*tert*-butyldimethylsilyloxy)pent-2-ene (218)



To a stirred solution of alcohol **217** (2.85 g, 8.23 mmol) in DCM (80 mL) at 0 °C was added triphenylphosphine (2.37 g, 9.04 mmol), followed by *N*-bromsuccinimide (1.54 g, 8.65 mmol) portionwise over a few minutes and the solution stirred at rt for 3 h. The reaction was quenched with H_2O (100 mL) and the organic material extracted with DCM (3 × 100 mL), washed with brine (170 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 24:1) afforded bromide **218** (2.37 g, 71%) as a colourless oil: $[\alpha]_D^{19}$ –18.7 (*c* 0.73 in $CHCl_3$); υ_{max}/cm^{-1} (thin film) 2929; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60 (12H, m, 2 × Si(C**H**$_3$)$_2$), 0.89 (9H, s) and 0.90 (9H, s, 2 × C(C**H**$_3$)$_3$), 3.42 (1H, dd, *J* 9.9, 6.2 Hz, TBSOC**H**H), 3.54 (1H, dd, *J* 9.9, 6.2 Hz, TBSOCH**H**), 3.96 (2H, d, *J* 7.2 Hz, BrC**H**$_2$), 4.19 (1H, m, TBSOC**H**), 5.75 (1H, dd, *J* 15.3, 5.0 Hz, BrCH$_2$CH=C**H**), 5.91 (1H, m, BrCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –4.7 and –4.6 (2 × Si(**C**H$_3$)$_2$), 18.3 and 18.4 (2 × **C**Me$_3$), 25.9 and 26.0 (2 × C(**C**H$_3$)$_3$), 32.5 (Br**C**H$_2$), 67.7 (TBSO**C**H$_2$), 73.0 (TBSO**C**H), 126.7 (BrCH$_2$**C**H=CH), 136.0 (BrCH$_2$CH=**C**H); *m/z* (EI$^+$) 431/433 (MNa$^+$, 12/13%), 351/353 (40/40), 330 (38), 329 (84), 307 (45), 197 (56), 189 (61), 177 (81), 176 (100). HRMS found 431.1418, $C_{17}H_{37}{}^{79}BrO_2Si_2Na$ (MNa$^+$) requires 431.1413.

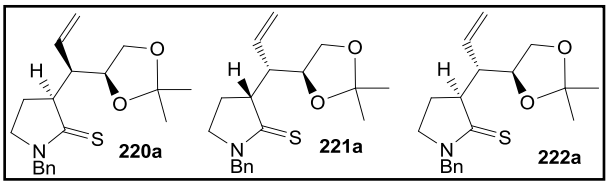
1-Benzylpyrrolidine-2-thione (219)[71]



To a solution of lactam **102** (4.57 mL, 28.5 mmol) in THF (90 mL) was added Lawesson's reagent (6.35 g, 15.7 mmol) and the solution heated to 40 °C with stirring for 2 h. After allowing the mixture to reach rt, the reaction was quenched with H_2O (60 mL) and the organic material extracted with EtOAc (3 × 100 mL), washed with brine (3 × 60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 2:1) afforded thiolactam **219** (3.90 g, 72%) as a pale yellow solid: mpt. 72-73 °C [lit.[126] 70-72 °C]; υ_{max}/cm^{-1} (solid) 2945, 1636, 1504; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (4H, quin, *J* 7.8 Hz, NCH$_2$C**H**$_2$), 3.07 (2H, t, *J* 7.8 Hz, C**H**$_2$C=S), 3.56 (2H, t, *J* 7.8 Hz, NC**H**$_2$), 4.96 (2H, s, NC**H**$_2$Ph), 7.24-7.34 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4 (NCH$_2$**C**H$_2$), 44.9

(**C**H_2C=S), 51.6 (N**C**H_2Ph), 54.0 (N**C**H_2), 128.0, 128.3 and 128.8 (Aromatic **C**H), 135.1 (NCH_2**C**), 201.7 (**C**=S).

(*S*)-1-Benzyl-3-((*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (220a), **(*R*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) allyl)pyrrolidine-2-thione (221a)** and **(*S*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (222a)**



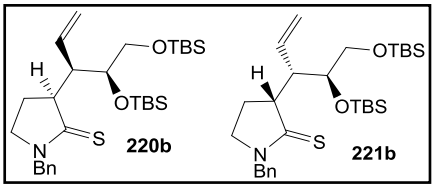
A mixture of thioamide **219** (0.59 g, 3.08 mmol), *E*-bromide **207** (0.75 g, 3.41 mmol) and 4Å molecular sieves (0.75 g) in MeCN (5 mL) was stirred under an argon atmosphere for 3 d. Further MeCN (10 mL) was added and the mixture warmed to 35 °C. Triethylamine (0.48 mL, 3.44 mmol) was added and the resulting solution stirred at 35 °C for 5 h. The mixture was cooled to rt, diluted with DCM (150 mL), washed with 2% citric acid (2 × 200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol:EtOAc 19:1) afforded rearrangement products **220a** (390 mg, 38%), **221a** (107 mg, 10%) and **222a** (10 mg, 1%), all as a pale yellow oils:

For **220a**: $[\alpha]_D^{17}$ –5.6 (*c* 0.68 in $CHCl_3$); υ_{max}/cm^{-1} (thin film) 3067, 2931, 1638, 1505, 1585; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (3H, s) and 1.31 (3H, s, C(C**H**$_3$)$_2$), 2.10 (1H, m) and 2.26 (1H, m, NCH_2C**H**$_2$), 3.02 (1H, m, CH_2=CHC**H**), 3.11 (1H, m, NC=SC**H**), 3.44 (1H, m) and 3.59 (1H, m, NC**H**$_2$CH_2), 3.61 (1H, t, *J* 7.9 Hz) and 4.02 (1H, dd, *J* 8.0, 6.4 Hz, OC**H**$_2$), 4.26 (1H, m, OC**H**), 4.80 (1H, d, *J* 14.3 Hz, NC**H**HPh), 5.19 (1H, dd, *J* 10.2, 1.8 Hz, C**H**H=CH), 5.22 (1H, dd, *J* 17.4, 1.8 Hz, CH**H**=CH), 5.25 (1H, d, *J* 14.3 Hz, NCH**H**Ph), 5.93 (1H, ddd, *J* 17.4, 10.2, 9.1 Hz, CH_2=C**H**), 7.30 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.4 (NCH_2**C**H_2), 25.4 and 26.3 (C(**C**H_3)$_2$), 47.7 (CH_2=CH**C**H), 51.8 (N**C**H_2Ph), 52.9 (N**C**H_2), 58.0 (NC=S**C**H), 68.0 (O**C**H_2), 74.5 (O**C**H), 109.1 (**C**Me$_2$), 118.7 (**C**H_2=CH), 128.0, 128.3 and 128.8 (Aromatic **C**H), 135.0 (Aromatic **C**), 135.1 (CH_2=**C**H), 205.4 (**C**=S); *m*/*z* (CI) 332 (MH^+, 31%), 316 (24), 275 (37), 230 (80), 191 (100), 91 (40); HRMS found 332.1677, $C_{19}H_{26}NO_2S$ (MH^+) requires 332.1684.

For **221a**: $[\alpha]_D^{22}$ +82.2 (*c* 0.60 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2983, 2931, 2873, 1637, 1503, 1452; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (3H, s) and 1.39 (3H, s, $C(CH_3)_2$), 1.85 (1H, m) and 2.17 (1H, m, NCH_2CH_2), 2.60 (1H, m, CH_2=CHC**H**), 3.41 (1H, m, NC=SC**H**), 3.48-3.52 (2H, m, NCH_2CH_2), 3.57 (1H, dd, *J* 8.2, 6.7 Hz) and 3.94 (1H, dd, *J* 8.2, 6.1 Hz, OCH_2), 4.91 (1H, d, *J* 14.4 Hz, NC**H**HPh), 4.99 (1H, m, OC**H**), 5.02 (1H, d, *J* 14.4 Hz, NCH**H**Ph), 5.06 (1H, dd, *J* 10.3, 1.6 Hz, C**H**H=CH), 5.16 (1H, dd, *J* 17.2, 1.0 Hz, CH**H**=CH), 5.76 (1H, ddd, *J* 17.2, 10.3, 9.5 Hz, CH_2=C**H**), 7.26-7.32 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.5 (NCH_2CH_2), 25.8 and 27.1 ($C(CH_3)_2$), 51.5 (NCH_2Ph), 52.6 (NC=SCH), 53.1 (CH_2=CHCH), 54.2 (NCH_2), 68.7 (OCH_2), 75.1 (OCH), 109.3 (CMe_2), 119.2 (CH_2=CH), 128.0, 128.4 and 128.8 (Aromatic CH), 135.0 (CH_2=CH), 135.3 (Aromatic **C**), 202.7 (C=S); *m/z* (CI) 332 (MH^+, 22%), 274 (100). HRMS found 332.1676, $C_{19}H_{26}NO_2S$ (MH^+) requires 332.1684.

For **222a**: $[\alpha]_D^{22}$ −27.7 (*c* 1.35, $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2981, 2920, 1644; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (3H, s) and 1.46 (3H, s, $C(CH_3)_2$), 1.97 (1H, m) and 2.15 (1H, m, NCH_2CH_2), 3.34 (1H, dt, *J* 8.4, 3.0 Hz, CH_2=CHC**H**), 3.42-3.53 (3H, m, NC=SC**H** and NCH_2CH_2), 3.74 (1H, dd, *J* 8.0, 5.8 Hz) and 4.05 (1H, m, OCH_2), 4.07 (1H, m, OC**H**), 4.89 (1H, d, *J* 14.3 Hz) and 5.09 (1H, d, *J* 14.3 Hz, NCH_2Ph), 5.12 (1H, dd, *J* 10.6, 1.2 Hz) and 5.23 (1H, dd, *J* 17.3, 1.2 Hz, CH_2=CH), 5.54 (1H, ddd, *J* 17.3, 10.6, 8.4 Hz, CH_2=C**H**), 7.27-7.32 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5 (NCH_2CH_2), 25.8 and 27.1 ($C(CH_3)_2$), 49.6 (CH_2=CHCH), 51.8 (NCH_2Ph), 52.8 (NCH_2), 54.7 (NC=SCH), 68.7 (OCH_2), 74.8 (OCH), 109.5 (CMe_2), 120.2 (CH_2=CH), 128.0, 128.4 and 128.8 (Aromatic CH), 133.0 (CH_2=CH), 135.2 (Aromatic **C**), 204.0 (C=S); *m/z* (EI) 331 (M^+, 16%), 316 (14), 91 (12), 65 (19), 55 (21), 51 (100); HRMS found 331.1605, $C_{19}H_{25}NO_2S$ (M^+) requires 331.1601.

(*S*)-3-((3*R*,4*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)pent-1-en-3-yl)-1-benzylpyrrolidine-2-thione (220b) and **(*R*)-3-((3*S*,4*S*)-4,5-bis (*tert*-butyldimethylsilyloxy)pent-1-en-3-yl)-1-benzylpyrrolidine-2-thione (221b)**



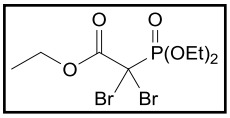
A mixture of thioamide **219** (0.21 g, 1.10 mmol), bromide **218** (0.50 g, 1.22 mmol) and 4Å molecular sieves (0.50 g) in MeCN (3 mL) was stirred under an argon atmosphere for 5 d; further MeCN was added (6 mL) and the mixture warmed to 35 °C. Triethylamine (123 mg, 0.17 mL, 1.22 mmol) was added and the resulting solution stirred at 35 °C for 7 h. The mixture was cooled to rt, diluted with DCM (100 mL), washed with 2% citric acid (2 × 150 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash chromatography (SiO_2, petrol/EtOAc 199:1 to 9:1) afforded **220b** (220 mg, 38%) as a white solid and **221b** (7.00 mg, 1%) as a yellow oil:

For **220b**: mpt. 51-52 °C; $[\alpha]_D^{17}$ –14.0 (*c* 0.88 in $CHCl_3$); υ_{max}/cm^{-1} (solid) 2932, 1630; ^{1}H NMR ($CDCl_3$, 500 MHz) δ –0.05 (3H, s) and –0.03 (9H, m, 2 × Si(C**H**$_3$)$_2$), 0.83 (9H, s) and 0.86 (9H, s, 2 × C(C**H**$_3$)$_3$), 2.02-2.11 (2H, m, NCH$_2$C**H**$_2$), 2.76 (1H, m, CH$_2$=CHC**H**), 3.26 (1H, m, NC=SC**H**), 3.37 (1H, m, NC**H**HCH$_2$), 3.47 (1H, m, NCH**H**CH$_2$), 3.59 (1H, dd, *J* 10.5, 4.8 Hz, OC**H**H), 3.78 (1H, dd, *J* 10.5, 4.4 Hz, OCH**H**), 4.27 (1H, m, OC**H**), 4.83 (1H, d, *J* 14.3 Hz, NC**H**HPh), 5.05 (1H, dd, *J* 9.7, 1.7 Hz, C**H**H=CH), 5.06 (1H, d, *J* 16.3 Hz, CH**H**=CH), 5.11 (1H, *J* 14.3 Hz, NCH**H**Ph), 5.92 (1H, td, *J* 16.3, 9.7 Hz, CH$_2$=C**H**), 7.29 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.3, –5.2, –4.6 and –3.7 (2 × Si(**C**H$_3$)$_2$), 18.2 and 18.3 (2 × **C**Me$_3$), 24.5 (NCH$_2$**C**H$_2$), 26.0 (2 × C(**C**H$_3$)$_3$), 49.7 (CH$_2$=CH**C**H), 51.5 (N**C**H$_2$Ph), 52.2 (N**C**H$_2$), 56.0 (C=S**C**H), 66.0 (O**C**H$_2$), 72.8 (O**C**H), 117.8 (**C**H$_2$=CH), 127.9, 128.3 and 128.8 (Aromatic **C**H), 135.3 (Aromatic **C**), 136.9 (CH$_2$=**C**H), 203.3 (**C**=S); *m/z* (CI) 520 (MH$^+$, 18%), 504 (25), 462 (44), 388 (100), 330 (11), 230 (54), 191 (33), 91 (34); HRMS found 520.3115, $C_{28}H_{50}NO_2SSi_2$ (MH$^+$) requires 520.3101.

For **221b**: $[\alpha]_D^{20}$ +14.0 (*c* 0.30 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2928, 1624; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (3H, s), 0.01 (3H, s), 0.17 (3H, s) and 0.22 (3H, s, 2 × Si(C**H**$_3$)$_2$), 0.89 (9H, s) and 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.84 (1H, m) and 2.17 (1H, m, NCH$_2$C**H**$_2$), 2.42 (1H, td, *J* 9.9, 2.1 Hz, CH$_2$=CHC**H**), 3.36 (1H, m, NC=SC**H**), 3.45

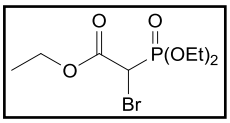
(1H, m, NC**H**HCH$_2$), 3.47 (1H, dd, *J* 10.7, 4.1 Hz, OC**H**H), 3.63 (1H, m, NCH**H**CH$_2$), 3.67 (1H, dd, *J* 10.7, 2.5 Hz, OCH**H**), 4.85 (1H, d, *J* 14.7 Hz, NC**H**HPh), 4.87 (1H, m, OC**H**), 5.02 (1H, dd, *J* 10.2, 2.2 Hz, C**H**H=CH), 5.06 (1H, d, *J* 14.7 Hz, NCH**H**Ph), 5.07 (1H, dd, *J* 17.3, 2.2 Hz, CH**H**=CH), 5.90 (1H, ddd, *J* 17.3, 10.2, 7.3 Hz, CH$_2$=C**H**), 7.30 (5H, m, Aromatic C**H**); ^{13}C NMR (CDCl$_3$, 125 MHz) δ –4.0 and –3.9 (2 × Si(**C**H$_3$)$_2$), 18.4 and 18.5 (2 × CMe$_3$), 26.0 and 26.1 (2 × C(**C**H$_3$)$_3$), 26.3 (NCH$_2$**C**H$_2$), 51.3 (N**C**H$_2$Ph), 52.2 (N**C**H$_2$), 52.4 (C=S**C**H), 53.2 (CH$_2$=CH**C**H), 66.3 (O**C**H$_2$), 72.9 (O**C**H), 118.5 (**C**H$_2$=CH), 127.9, 128.3 and 128.7 (Aromatic **C**H), 135.5 (Aromatic **C**), 136.0 (CH$_2$=**C**H), 202.9 (**C**=S); *m/z* (CI) 520 (MH$^+$, 100%), 504 (44), 388 (42). HRMS found 520.3110, $C_{28}H_{50}NO_2SSi_2$ (MH$^+$) requires 520.3101.

Triethyl dibromophosphonoacetate (226)[72]



To a solution of NaOH (20.0 g, 500 mmol) in H$_2$O (60 mL) at –10 °C was added Br$_2$ (12.8 mL, 250 mmol) dropwise over *ca.* 30 min. To this, phosphonate **225** (10.6 mL, 53.5 mmol) was added dropwise with the internal temperature being maintained below 10 °C. The product was extracted immediately with CHCl$_3$ (4 × 100 mL), washed with H$_2$O (2 × 20 mL), dried (MgSO$_4$) and the solvent removed *in vacuo* to give dibromide **226** (19.8 g, 97%) as a cloudy oil: υ_{max}/cm^{-1} (CDCl$_3$ cast) 2984, 2936, 1733; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.36 (3H, t, *J* 7.1 Hz, CO$_2$CH$_2$**C**H$_3$), 1.40 (6H, m, P=O(OCH$_2$C**H**$_3$)$_2$), 4.31-4.47 (6H, m, 3 × C**H**$_2$); ^{13}C NMR (CDCl$_3$, 125 MHz) 13.8 (C=OCH$_2$**C**H$_3$), 16.4 and 16.5 (P=O(OCH$_2$**C**H$_3$)$_2$), 46.4 (**C**Br$_2$), 64.7 (C=O**C**H$_2$CH$_3$), 66.4 and 66.5 (P=O(O**C**H$_2$CH$_3$)$_2$), 163.8 (**C**=O); *m/z* (CI) 381/383/385 (MH$^+$, 47/100/46%), 353/355/357 (16/32/16). HRMS found 380.9094, $C_8H_{16}{}^{79}Br_2O_5P$ (MH$^+$) requires 380.9102.

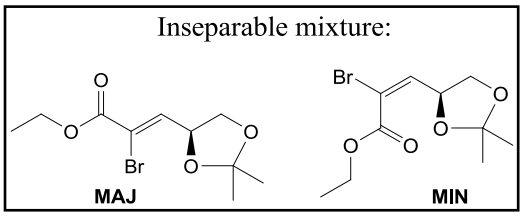
Triethyl bromophosphonoacetate (227)[72]



To a solution of dibromide **226** (18.6 g, 48.5 mmol) in EtOH (45 mL) at –10 °C was added a solution of SnCl$_2$ (7.80 g, 41.1 mmol) in H$_2$O (95 mL) was added over *ca.* 20 min with the internal temperature being maintained at –10 °C. The product was extracted immediately with CHCl$_3$ (4 × 100 mL), dried (MgSO$_4$) and the solvent removed *in vacuo* to give phosphonate **227** (13.5 g, 92%) as a

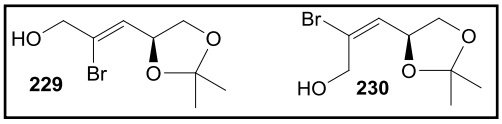
colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2982, 1741; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (3H, t, *J* 7.2 Hz, C=O$CH_2C\mathbf{H}_3$), 1.35 (6H, t, *J* 7.1 Hz, P=O($OCH_2C\mathbf{H}_3)_2$), 4.20-4.28 (6H, m, 3 × $C\mathbf{H}_2$), 4.34 (1H, d, *J* 14.0 Hz, C**H**Br); ^{13}C NMR ($CDCl_3$, 125 MHz) 14.0 (C=O$CH_2\mathbf{C}H_3$), 16.4 (P=O$CH_2\mathbf{C}H_3$), 36.5 (**C**Br), 63.2 and 64.7 (C=O**C**H_2CH_3 and P=O(O**C**$H_2CH_3)_2$), 165.1 (**C**=O); *m/z* (FAB^+) 325/327 (MNa^+, 98/100%), 303 (31), 247 (30). HRMS found 324.9810, $C_8H_{16}{}^{79}BrO_5PNa$ (MNa^+) requires 324.9816.

(*S*,*Z*)-Ethyl 2-bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate and
(*S*,*E*)-ethyl 2-bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (228) - inseparable mixture



To a solution of diacetonide **210** (2.49 g, 9.50 mmol) in aq. $NaHCO_3$ (5% w/v, 25 mL) at 0 °C was added a solution of $NaIO_4$ (2.48 g, 11.4 mmol) in H_2O (25 mL). After stirring for 1 h, the solution was cooled to 0 °C and then phosphonate **227** (12.0 g, 39.4 mmol) and K_2CO_3 (6 M, 70 mL) were added successively and the reaction stirred overnight at rt. After dissolving any remaining solid in H_2O (*ca*. 50 mL), the organic material was extracted with DCM (3 × 150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 98:2) afforded an inseparable 1.6:1 mixture of *Z*:*E* ester **228** (4.57 g, 86%) as a colourless oil: ν_{max}/cm^{-1} ($CDCl_3$ cast) 2985, 2935, 1783, 1729, 1631; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30-1.40 (6H, m, $C\mathbf{H}_3CH_2$ of MAJ and $C\mathbf{H}_3CH_2$ of MIN), 1.33 (3H, s) and 1.37 (3H, s, $C(C\mathbf{H}_3)_2$ of MIN), 1.41 (3H, s) and 1.46 (3H, s, $C(C\mathbf{H}_3)_2$ of MAJ) 3.71 and 4.20-4.35 (8H, m, $OC\mathbf{H}_2CH$ of MAJ, $OC\mathbf{H}_2CH$ of MIN, $OC\mathbf{H}_2CH_3$ of MAJ and $OC\mathbf{H}_2CH_3$ of MIN), 4.95 (1H, q, *J* 6.7 Hz, OC**H** of MAJ), 5.22 (1H, q, *J* 7.3 Hz, OC**H** of MIN), 6.80 (1H, d, *J* 6.9 Hz, BrC=C**H** of MIN), 7.36 (1H, d, *J* 6.7 Hz, BrC=C**H** of MAJ); *m/z* (CI) 279/281 (MH^+, 8/5%), 263/265 (100/100). HRMS found 279.0229, $C_{10}H_{16}{}^{79}BrO_4$ (MH^+) requires 279.0226.

(*S*,*Z*)-2-Bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (229) and **(*S*,*E*)-2-Bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (230)**

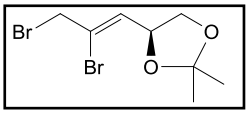


To a solution of *E*- and *Z*-esters **228** (3.15 g, 11.3 mmol) in DCM (30 mL) at −78 °C was added DIBAL (1.2 M in toluene, 22.7 mL, 27.2 mmol) dropwise and the solution stirred for 6 h at −78 °C. After allowing the reaction mixture to warm to rt, MeOH (50 mL), Et_2O (60 mL) and aq. sat. Rochelle's salt (60 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (50 mL), organic material extracted with EtOAc (3 × 50 mL), washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded *E*-alcohol **229** (1.35 g, 41% from **210**) and *Z*-alcohol **230** (0.81 g, 25% from **210**) as colourless oils:

For **229**: $[\alpha]_D^{22}$ = +12.1 (*c* 1.34 in $CHCl_3$); ν_{max}/cm^{-1} (DCM cast) 3439 br, 2987, 2929, 2869, 1667; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (3H, s) and 1.44 (3H, s, C(C**H**$_3$)$_2$), 3.65 (1H, dd, *J* 8.3, 7.1 Hz) and 4.22 (1H, dd, *J* 8.3, 6.3 Hz, OC**H**$_2$), 4.25 (2H, s, C**H**$_2$OH), 4.92 (1H, td, *J* 7.1, 6.3 Hz, OC**H**), 6.20 (1H, d, *J* 7.3 Hz, BrC=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) 25.7 and 26.6 (C(**C**H$_3$)$_2$), 67.8 (O**C**H$_2$), 68.6 (**C**H$_2$OH), 75.2 (O**C**H), 109.7 (**C**Me$_2$), 128.0 (BrC=**C**H), 129.0 (Br**C**=CH); *m/z* (CI) 237/239 (MH^+, 56/52%) 221/223 (30/23), 196/198 (98/100); HRMS found 237.0119, $C_8H_{14}{}^{79}BrO_3$ (MH^+) requires 237.0121.

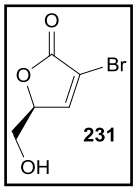
For **230**: ν_{max}/cm^{-1} (DCM cast) 3421 br, 2976, 2903, 1665; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (3H, s) and 1.40 (3H, s, C(C**H**$_3$)$_2$), 3.62 (1H, dd, *J* 8.4, 7.1 Hz) and 4.10 (1H, dd, *J* 8.4, 6.3 Hz, OC**H**$_2$), 4.40 (2H, s, C**H**$_2$OH), 4.83 (1H, ddd, *J* 8.2, 7.1, 6.3 Hz, OC**H**), 6.05 (1H, d, *J* 8.2 Hz, BrC=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) 25.8 and 26.7 (C(**C**H$_3$)$_2$), 63.8 (**C**H$_2$OH), 69.2 (O**C**H$_2$), 72.6 (O**C**H), 110.0 (**C**Me$_2$), 129.6 (**C**Br) 132.3 (BrC=**C**H).

(*S*,*Z*)-4-(2,3-Dibromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (223)



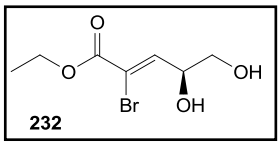
To a solution of alcohol **229** (0.95 g, 4.03 mmol) in DCM (35 mL) at 0 °C was added triphenylphosphine (1.16 g, 4.42 mmol), followed by *N*-bromosuccinimide (0.75 g, 4.21 mmol) portionwise over a few minutes and the solution was stirred at rt for 3 h. The reaction was quenched with H_2O (50 mL), organic material extracted with DCM (3 × 50 mL), washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 23:2) afforded bromide **223** (0.80 g, 67%) as a yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2986, 2932, 1647; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (3H, s) and 1.42 (3H, s, C(C**H**$_3$)$_2$), 3.65 (1H, dd, *J* 8.4, 6.8 Hz, OC**H**H), 4.20 (1H, d, *J* 11.7 Hz, C**H**HBr), 4.23 (1H, d, *J* 11.7 Hz, CH**H**Br), 4.24 (1H, dd, *J* 8.4, 6.4 Hz, OCH**H**), 4.85 (1H, app. q, *J* 6.9 Hz, OC**H**), 6.27 (1H, d, *J* 7.1 Hz, BrC=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) 25.6 and 26.6 (C(**C**H$_3$)$_2$), 37.4 (**C**H$_2$Br), 68.4 (O**C**H$_2$), 75.7 (O**C**H), 110.0 (**C**Me$_2$), 124.2 (**C**Br), 132.7 (BrC=**C**H); *m/z* (CI) 299/301/303 (MH^+, 28/52/22%), 241/243/245 (27/53/23) 219/221 (27/27), 189/191 (50/50), 161/163 (100/99). HRMS found 298.9289, $C_8H_{13}{}^{79}Br_2O_2$ (MH^+) requires 298.9282.

3-Bromo-5-(hydroxymethyl)furan-2(5H)-one (231) and **(*S*,*Z*)-ethyl 2-bromo-4,5-dihydroxypent-2-enoate (232)**



Ester mixture **228** (3.20 g, 11.5 mmol) and 60% aq. AcOH (60 mL) were stirred at rt for 2 d. Petrol (60 mL) was added, the aq. layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 60 mL) and toluene (3 × 60 mL) to give lactone **231** (0.76 g, 35% from **210**) as a yellow oil: $[\alpha]_D^{20}$ +27.0 (*c* 0.91 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3397br, 2984, 1713, 1627; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (3H, t, *J* 7.2 Hz, C**H**$_3$), 3.65 (1H, dd, *J* 11.2, 7.2 Hz, C**H**HOH), 3.83 (1H, dd, *J* 11.2, 3.2 Hz, CH**H**OH), 4.30 (2H, q, *J* 7.2 Hz, CH$_3$C**H**$_2$), 4.71 (1H, td, *J* 7.2, 3.2 Hz, C**H**OH), 7.30 (1H, d, *J* 7.6 Hz, CBr=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (**C**H$_3$), 63.0 (CH$_3$**C**H$_2$), 64.1 (**C**H$_2$OH), 72.6 (**C**HOH), 117.4 (**C**Br), 143.2 (CBr=**C**H), 161.9 (**C**=O); *m/z* (CI) 239/241 (MH^+, 8/7%), 223 (97), 221 (100), 195 (45), 193 (48), 177 (93), 175 (94). HRMS found 238.9915, $C_7H_{12}{}^{79}BrO_4$ (MH^+) requires 238.9919.

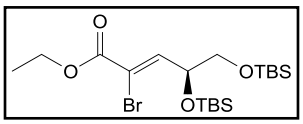
Further elution gave diol **232** (1.49 g, 6.26 mmol, 54% from **210**) as a colourless oil: $[\alpha]_D^{20}$ –51.5 (*c* 0.20 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3400br, 2930, 1756, 1607; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.83 (1H, dd, *J* 12.3, 4.8 Hz, C**H**H), 3.99 (1H, dd, *J* 12.3, 3.9 Hz, CH**H**), 5.08 (1H, ddd, *J* 4.8, 3.9, 1.8 Hz, CH_2C**H**), 7.54 (1H, d, *J* 1.8 Hz, CBr=C**H**); ^{13}C NMR ($CDCl_3$, 125MHz) δ 62.2 (**C**H_2), 83.2 (CH_2**C**H), 114.5 (**C**Br), 150.0 (CBr=**C**H) 168.3 (**C**=O); *m*/*z* (CI) 193/195 (MH^+, 46/46%), 177 (99), 175 (100). HRMS found 192.9495, $C_5H_6{}^{79}BrO_3$ (MH^+) requires 192.9500.



232

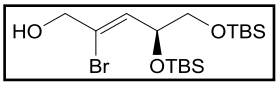
(*S*,*Z*)-Ethyl 2-bromo-4,5-bis(*tert*-butyldimethylsilyloxy)pent-2-enoate (233)

To a solution of diol **232** (1.23 g, 5.17 mmol) and imidazole (1.75 g, 25.7 mmol) in DCM (30 mL) at 0 °C was added TBSCl (2.33 g, 15.4 mmol) and the solution stirred for 3 h at rt. The reaction was quenched with H_2O (50 mL), the organic material extracted with DCM (3 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded ester **233** (2.09 g, 87%) as a colourless oil: $[\alpha]_D^{20}$ +1.9 (*c* 0.57 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2955, 2929, 2886, 2858, 1723, 1630; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (9H, m) and 0.07 (3H, s, 2 × Si(C**H**$_3$)$_2$), 0.86 (18H, s, 2 × C(C**H**$_3$)$_3$), 1.31 (3H, t, *J* 7.1 Hz, C**H**$_3$CH_2), 3.56 (1H, dd, *J* 10.3, 4.9 Hz, TBSOCH**H**), 3.63 (1H, dd, *J* 10.3, 6.3 Hz, TBSOC**H**H), 4.30 (2H, q, *J* 7.1 Hz, CH_3C**H**$_2$), 4.62 (1H, ddd, *J* 8.0, 6.3, 4.9 Hz, TBSOC**H**), 7.12 (1H, d, *J* 8.0 Hz, CBr=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.5 and –4.6 (2 x Si(**C**H_3)$_2$)), 14.2 (**C**H_3CH_2), 25.8, 25.9, 26.0 (2 x C(**C**H_3)$_3$), 62.7 (CH_3**C**H_2), 66.2 (TBSO**C**H_2), 74.1 (TBSO**C**H), 115.8 (**C**Br) 145.9 (CBr=**C**H), 162.2 (**C**=O); *m*/*z* (CI) 467/469 (MH^+, 2/3%), 335/337 (100/99). HRMS found 467.1637, $C_{19}H_{40}{}^{79}BrO_4Si_2$ (MH^+) requires 467.1648.



(*S*,*Z*)-2-Bromo-4,5-bis(*tert*-butyldimethylsilyloxy)pent-2-en-1-ol (234)

To a solution of $LiAlH_4$ (1 M solution in THF, 1.18 mL, 1.18 mmol) in Et_2O (15 mL) at 0 °C was added a solution of ester **233** (500 mg, 1.07 mmol) in Et_2O (15 mL) over a few minutes; the solution was stirred at 0



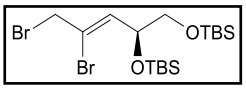
°C for 15 minutes. The reaction was quenched with H_2O (20 mL) and stirred for a further 30 minutes. The organic material was extracted with Et_2O (3 × 200 mL), washed with H_2O (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to afford alcohol **234** (403 mg, 91%) as a pale yellow oil: $[\alpha]_D^{20}$ +0.5 (*c* 0.78 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3369br, 2954, 2929, 2886, 2857, 1664; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07-0.11 (12H, m, 2 × Si(C**H**$_3$)$_2$), 0.90 and 0.91 (18H, 2 × C(C**H**$_3$)$_3$), 1.40 (1H, br s, O**H**), 3.55 (1H, dd, *J* 10.4, 5.1 Hz) and 3.60 (1H, dd, *J* 10.4, 6.4 Hz, TBSOC**H**$_2$), 4.23-4.28 (2H, m, C**H**$_2$OH), 4.56 (1H, m, TBSOC**H**), 5.99 (1H, d, *J* 7.6 Hz, CBr=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.5 and –4.5 (2 × Si(**C**H$_3$)$_2$), 18.2 and 18.5 (2 × **C**Me$_3$), 25.9 and 26.0 (2 × C(**C**H$_3$)$_3$), 66.8 (TBSO**C**H$_2$), 68.2 (**C**H$_2$OH), 73.6 (TBSO**C**H), 126.7 (**C**Br), 130.9 (CBr=**C**H); *m*/*z* (FAB$^+$) 447/449 (MNa$^+$, 41/40%), 369 (72), 367 (70), 295 (65), 293 (69), 189 (100). HRMS found 447.1370, $C_{17}H_{37}{}^{79}BrO_3Si_2Na$ (MNa$^+$) requires 447.1362.

Toluene-4-sulfonic acid 2-bromo-4,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-pent-2-enyl ester (236)

To a solution of alcohol **234** (120 mg, 0.28 mmol), triethylamine (120 μL, 0.86 mmol) and DMAP (5.20 mg, 42.6 μmol) in DCM (3 mL) at 0 °C was added TsCl (64.0 mg, 0.34 mmol), and the solution stirred for 5 h at rt. The solution was diluted with DCM (10 mL), washed successively with HCl (1 M, 5 mL), aq. sat. $NaHCO_3$ (5 mL) and brine (2 × 5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 99:1) afforded tosylate **236** (82.0 mg, 60%) as a colourless oil: $[\alpha]_D^{20}$ –12.5 (*c* 0.42 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2954, 2929, 2857, 1599; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.02 (3H, s), 0.03 (6H, s) and 0.05 (3H, s, 4 × Si(C**H**$_3$)$_2$), 0.85 (9H, s) and 0.86 (9H, s, 2 × C(C**H**$_3$)$_3$), 2.46 (3H, s, PhC**H**$_3$), 3.46 (1H, dd, *J* 10.3, 4.9 Hz, TBSOC**H**H), 3.53 (1H, dd, *J* 10.3, 6.4 Hz, TBSOCH**H**), 4.47 (1H, ddd, *J* 7.7, 6.4, 4.9 Hz, OC**H**), 4.62 (1H, d, *J* 12.4 Hz) and 4.66 (1H, d, *J*, 12.4 Hz, C**H**$_2$OTs), 6.02 (1H, d, *J* 7.7 Hz, CBr=C**H**), 7.35 (2H, d, *J* 8.3 Hz) and 7.81 (2H, d, *J* 8.3 Hz, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.6 (2 x Si(**C**H$_3$)$_2$), 18.2 and 18.4 (2 x **C**Me$_3$), 21.8 (Ph**C**H$_3$), 25.9 and 26.0 (2 × C(**C**H$_3$)$_3$), 60.5 (TBSO**C**H$_2$), 73.3 (**C**H$_2$OPh) 73.5 (TBSO**C**H), 117.9 (Aromatic **C** or **C**Br=CH), 128.1 and 130.0 (Aromatic **C**H), 132.9 (Aromatic **C** or **C**Br=CH), 136.0

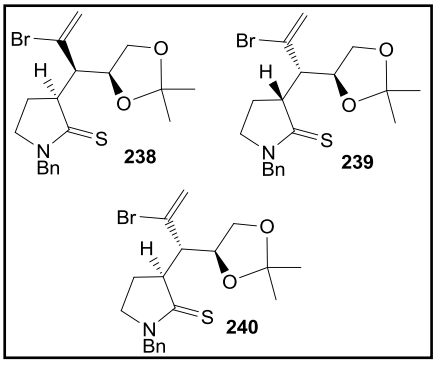
(CBr=**C**H), 145.2 (Aromatic **C** or **C**Br=CH); *m*/*z* (CI) 579/581 (MH^+, 8/8%), 449 (100), 447 (66), 409 (76), 407 (58), 345 (45), 277 (75). HRMS found 579.1647, $C_{24}H_{44}{}^{79}BrO_5SSi_2$ (MH^+) requires 579.1631.

(*S*,*Z*)-1,2-Dibromo-4,5-bis(*tert*-butyldimethylsilyloxy)pent-2-ene (224)



To a solution of tosylate **236** (0.51 g, 0.88 mmol) in MeCN (30 mL) at 0 °C was added LiBr (0.38 g, 4.42 mmol) and the solution stirred at rt for 24 h. After removal of the MeCN *in vacuo*, brine was added (30 mL) and the organic material extracted with EtOAc (2 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield dibromide **224** (250 mg, 60%) as a colourless oil: $[\alpha]_D^{20}$ +38.4 (*c* 0.85 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2954, 2929, 2857; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.04-0.10 (12H, m, 2 × Si(C**H**$_3$)$_2$), 0.88 (9H, s) and 0.89 (9H, s, 2 × C(C**H**$_3$)$_3$), 3.53 (1H, dd, *J* 10.3, 5.2 Hz, OC**H**H), 3.59 (1H, dd, *J* 10.3, 6.2 Hz, OCH**H**), 4.18 (1H, dd, *J* 11.3, 0.6 Hz, CH**H**Br), 4.23 (1H, dd, *J* 11.3, 0.5, Hz, C**H**HBr), 4.49 (1H, m, OC**H**), 6.05 (1H, d, *J* 7.9 Hz, CBr=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.6 and −4.4 (2 × Si(**C**H$_3$)$_2$), 18.2 and 18.5 (2 × **C**Me$_3$), 25.9 and 26.0 (2 × C(**C**H$_3$)$_3$), 38.1 (**C**H$_2$Br), 66.5 (O**C**H$_2$), 74.0 (O**C**H), 122.3 (CBr), 135.4 (C(Br)=**C**H); *m*/*z* (EI) 429/431/433 ([M−^{t}Bu]$^+$, 6/11/6%), 207 (22), 205 (17), 189 (30), 148 (15), 147 (100). HRMS found 428.9903, $C_{17}H_{27}{}^{79}Br_2O_2Si_2$ ([M−^{t}Bu]$^+$) requires 428.9916.

(*S*)-1-Benzyl-3-((*R*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (238) **(*R*)-1-benzyl-3-((*S*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (239)** and **(*S*)-1-benzyl-3-((*S*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (240)**



A mixture of thioamide **219** (116 mg, 0.61 mmol), *Z*-bromide **223** (200 mg, 0.67 mmol) and 4Å molecular sieves (250 mg) in MeCN (1 mL) was stirred under an argon atmosphere for 4 d. Further MeCN (2 mL) was added and the mixture warmed to 35 °C. Triethylamine (94.0 μL, 0.67 mmol) was added and the resulting solution stirred at 35 °C for 7 h. The mixture was cooled to rt,

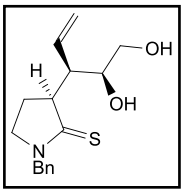
diluted with DCM (30 mL), washed with 2% citric acid (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded successive products **238** (130 mg, 52%) as a pale yellow oil, **239** (6.0 mg, 2%) as a colourless oil and **240** (5.0 mg, 2%) as a colourless oil:

For **238**: $[\alpha]_D^{20}$ –33.5 (*c* 0.65 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2985, 2883, 1625, 1507, 1452, 1311; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (3H, s) and 1.40 (3H, s, C(C**H**$_3$)$_2$), 2.20 (1H, m) and 2.30 (1H, m, NCH$_2$C**H**$_2$), 3.34 (1H, m, C=SC**H**), 3.48 (1H, m, NC**H**HCH$_2$), 3.58-3.62 (2H, m, CH$_2$=CBrC**H** and NCH**H**CH$_2$), 3.88 (1H, t, *J* 8.1 Hz) and 4.01 (1H, dd, *J* 8.1, 6.4 Hz, OC**H**$_2$), 4.41 (1H, ddd, *J* 8.1, 6.4, 5.6 Hz, OC**H**), 4.87 (1H, d, *J* 14.3 Hz) and 5.15 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 5.66 (1H, d, *J* 1.8 Hz) and 6.07 (1H, dd, *J* 1.8, 0.6 Hz, C**H**$_2$=CBr), 7.30-7.35 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (NCH$_2$**C**H$_2$), 25.2 and 26.6 (C(**C**H$_3$)$_2$), 52.2 (N**C**H$_2$Ph), 52.5 (N**C**H$_2$CH$_2$), 52.9 (CH$_2$=CBr**C**H), 56.3 (C=S**C**H), 67.2 (O**C**H$_2$), 74.6 (O**C**H), 109.2 (**C**Me$_2$), 121.0 (**C**H$_2$=CBr), 128.2, 128.5, 129.0 (Aromatic **C**H), 131.8 (**C**Br), 135.0 (Aromatic **C**), 201.7 (**C**=S); *m/z* (CI) 410/412 (MH^+, 24/26%), 338/340 (79/79), 141 (100). HRMS found 410.0774, $C_{19}H_{25}{}^{79}BrNO_2S$ (MH^+) requires 410.0789.

For **239**: $[\alpha]_D^{20}$ +31.5 (*c* 1.08 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2983, 2934, 2874, 1625, 1499, 1452, 1316; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (3H, s) and 1.34 (3H, s, C(C**H**$_3$)$_2$), 2.30-2.40 (2H, m, NCH$_2$C**H**$_2$), 3.21 (1H, t, *J* 8.5 Hz, C=SC**H**), 3.51 (1H, ddd, *J* 11.0, 8.5, 7.0 Hz) and 3.62 (1H, ddd, *J* 11.0, 8.8, 5.2 Hz, NC**H**$_2$CH$_2$), 3.76 (1H, dd, *J* 8.5, 6.8 Hz, OC**H**H), 3.88 (1H, dd, *J* 10.1, 1.8 Hz, CH$_2$=CBrC**H**), 4.10 (1H, dd, *J* 8.5, 6.1 Hz, OCH**H**), 4.44 (1H, ddd, *J* 10.1, 6.8, 6.1 Hz, OC**H**), 4.79 (1H, d, *J* 14.6 Hz) and 5.16 (1H, d, *J* 14.6 Hz, NC**H**$_2$Ph), 5.51 (1H, dd, *J* 1.8, 0.5 Hz) and 5.90 (1H, dd, *J* 1.8, 0.4 Hz, C**H**$_2$=CBr), 7.26-7.32 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.2 (NCH$_2$**C**H$_2$), 26.0 and 26.5 (C(**C**H$_3$)$_2$), 51.9 (N**C**H$_2$Ph), 52.8 (N**C**H$_2$CH$_2$), 55.2 (CH$_2$=CBr**C**H), 56.9 (C=S**C**H), 68.7 (O**C**H$_2$), 74.7 (O**C**H), 110.1 (**C**Me$_2$), 119.8 (**C**H$_2$=CBr), 127.9, 128.2, 128.7 (Aromatic **C**H), 133.5 (**C**Br), 135.3 (Aromatic **C**), 203.7 (**C**=S); *m/z* (CI) 410/412 (MH^+, 16/14%), 352/354 (46/50), 338/340 (63/63), 330 ($[MH-HBr]^+$, 100). HRMS found 410.0800, $C_{19}H_{25}{}^{79}BrNO_2S$ (MH^+) requires 410.0790.

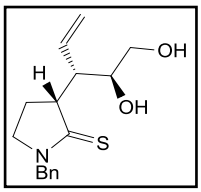
For **240**: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2984, 2932, 2877, 1615, 1507, 1453; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37 (3H, s) and 1.49 (3H, s, C(C**H**$_3$)$_2$), 2.18 (1H, m) and 2.40 (1H, m, NCH$_2$C**H**$_2$), 3.48-3.69 (4H, m, C=SC**H**, CH$_2$=CBrC**H** and NC**H**$_2$CH$_2$), 3.82 (1H, dd, *J* 8.6, 5.0 Hz) and 4.15 (1H, dd, *J* 8.6, 6.2 Hz, OC**H**$_2$), 4.37 (1H, ddd, *J* 11.2, 6.2, 5.0 Hz, OC**H**), 4.91 (1H, d, *J* 14.4 Hz) and 5.08 (1H, d, *J* 14.4 Hz, NC**H**$_2$Ph), 5.55 (1H, d, *J* 1.6 Hz) and 6.04 (1H, d, *J* 1.6 Hz, C**H**$_2$=CBr), 7.29-7.34 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6 (NCH$_2$**C**H$_2$), 25.6 and 27.1 (C(**C**H$_3$)$_2$), 52.0 (N**C**H$_2$Ph), 52.7 (CH$_2$=CBrC**H**), 53.1 (N**C**H$_2$CH$_2$), 55.0 (C=S**C**H), 68.1 (O**C**H$_2$), 76.1 (O**C**H), 110.0 (**C**Me$_2$), 123.6 (**C**H$_2$=CBr), 128.1, 128.4 (Aromatic **C**H), 128.6 (**C**Br), 128.8 (Aromatic **C**H), 135.0 (Aromatic **C**), 202.9 (**C**=S); *m/z* (CI) 410/412 (MH^+, 2/2%), 183 (100) 141 (17), 119 (18). HRMS found 410.0786, $C_{19}H_{25}{}^{79}BrNO_2S$ (MH^+) requires 410.0789.

(*S*)-1-Benzyl-3-((2*S*,3*R*)-1,2-dihydroxypent-4-en-3-yl)pyrrolidine-2-thione (242)



Acetonide **220a** (270 mg, 0.82 mmol) and aq. AcOH (60% v/v, 15 mL) were stirred at rt for 24 h. Petrol (15 mL) was added and the aq. Layer was separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 15 mL) and toluene (3 × 15 mL) to give diol **242** (232 mg, 98%) as a pale yellow oil: $[\alpha]_D^{17}$ –159.3 (*c* 1.00 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3362br, 3069, 3030, 2922, 2878, 1637, 1510, 1452, 1310; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.03 (1H, m NCH$_2$C**H**H), 2.15 (1H, br s, O**H**), 2.22 (1H, m, NCH$_2$CH**H**), 2.58 (1H, m, CH$_2$=CHC**H**), 3.30 (1H, br t, *J* 8.3 Hz, NC=SC**H**), 3.45 (1H, m) and 3.53 (1H, m, NC**H**$_2$CH$_2$), 3.58 (2H, d, *J* 5.8 Hz, C**H**$_2$OH), 3.98 (1H, d, *J* 2.8 Hz, O**H**), 4.12 (1H, m, C**H**OH), 4.93 (1H, d, *J* 14.3 Hz) and 5.07 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 5.15 (1H, d, *J* 10.6 Hz) and 5.16 (1H, d, *J* 16.7 Hz, C**H**$_2$=CH), 5.96 (1H, ddd, *J* 16.7, 10.6, 9.7 Hz, CH$_2$=C**H**), 7.29-7.35 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9 (NCH$_2$**C**H$_2$), 50.2 (CH$_2$=CH**C**H)), 52.2 (N**C**H$_2$Ph), 52.8 (N**C**H$_2$CH$_2$), 58.5 (C=S**C**H), 65.3 (**C**H$_2$OH), 72.9 (**C**HOH), 119.8 (**C**H$_2$=CH), 128.3, 128.4, 129.0 (Aromatic **C**H), 134.4 (CH$_2$=**C**H), 134.8 (Aromatic **C**), 202.3 (**C**=S); *m/z* (CI) 292 (MH^+, 25%), 274 (10), 230 (32), 191 (78), 91 (100). HRMS found 292.1364, $C_{16}H_{22}NO_2S$ (MH^+) requires 292.1371.

(*R*)-1-Benzyl-3-((2*S*,3*S*)-1,2-dihydroxypent-4-en-3-yl)pyrrolidine-2-thione (243)

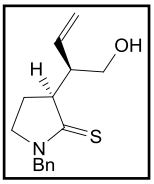


Acetonide **221a** (100 mg, 0.30 mmol) and aq. AcOH (60% v/v, 5 mL) were stirred at rt for 4 h. Petrol (5 mL) was added and the aq. layer was separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 5 mL) and toluene (3 × 5 mL). Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3) afforded diol **243** (80.0 mg, 92%) as a white solid: mpt 111-112 °C; $[\alpha]_D^{17}$ +10.3 (*c* 0.51 in $CHCl_3$); υ_{max}/cm^{-1} (solid) 3368br, 2920, 2873, 1630, 1518; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.85 (1H, m) and 2.22 (1H, m, NCH_2CH_2), 2.53 (1H, m, CH_2=CHC**H**), 3.40-3.51 (2H, m, NCH_2CH_2), 3.48 (1H, ddd, *J* 11.3, 6.8, 1.1 Hz, C**H**HOH), 3.59 (1H, m, NC=SC**H**), 3.68 (1H, ddd, *J* 11.3, 3.0, 1.0 Hz, CH**H**OH), 4.12 (1H, dddd, *J* 10.0, 6.8, 3.0, 1.0 Hz, C**H**OH), 4.88 (1H, d, *J* 14.3 Hz) and 5.02 (1H, d, *J* 14.3 Hz, NCH_2Ph), 5.06 (1H, dd, *J* 10.2, 0.7 Hz) and 5.20 (1H, dd, *J* 17.1, 0.7 Hz, CH_2=CH), 5.52 (1H, dtd, *J* 17.1, 10.2, 1.0 Hz, CH_2=C**H**), 7.28-7.34 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2 (NCH_2CH_2), 51.5 (CH_2=CH**C**H), 52.0 (N**C**H_2Ph), 53.3 (N**C**H_2CH_2), 54.2 (C=S**C**H), 64.8 (**C**H_2OH), 71.4 (**C**HOH), 120.0 (**C**H_2=CH), 128.3, 128.5, 129.0 (Aromatic **C**H), 134.9 (Aromatic **C**), 135.2 (CH_2=**C**H), 202.1 (**C**=S); *m*/*z* (CI) 292 (MH^+, 100%), 274 (31). HRMS found 292.1367, $C_{16}H_{22}NO_2S$ (MH^+) requires 292.1371.

(*S*)-1-Benzyl-3-((*R*)-1-hydroxybut-3-en-2-yl)pyrrolidine-2-thione (244)

Preparation of silica gel-supported $NaIO_4$:

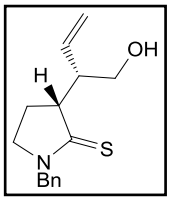
To a solution of $NaIO_4$ (2.57 g, 12.0 mmol) in hot H_2O (*ca*. 70 °C, 5 mL) was added SiO_2 (10.0 g) and the contents shaken vigorously until a free flowing powder had formed.



To a suspension of silica gel-supported $NaIO_4$ powder (0.32 g) in DCM (2 mL) was added a solution of diol **242** (102 mg, 0.35 mmol) in DCM (2 mL) and the mixture stirred for 1 h at rt. After removal of the solid by filtration, the DCM was removed by concentration *in vacuo* and the intermediate aldehyde was dissolved in an EtOH/THF mixture (2:1, 6 mL) and $NaBH_4$ (130 mg, 3.44 mmol) added. The solution was stirred for 15 minutes at rt, then HCl (1 M) added until

the mixture was neutral. The organic material was extracted with EtOAc (3 × 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3) afforded alcohol **244** (46.1 mg, 51%) as a pale yellow oil: $[\alpha]_D^{20}$ −73.2 (*c* 0.40 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3410br, 2923, 2875, 1639, 1508, 1452, 1309; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.87 (1H, ddt, *J* 12.8, 8.8, 6.1 Hz) and 2.17 (1H, dtd, *J* 12.8, 9.1, 5.9 Hz, NCH_2CH_2), 2.62 (1H, br s, O**H**), 3.02 (1H, m, CH_2=CHC**H**), 3.33 (1H, ddd, *J* 9.1, 6.3, 3.6 Hz, C=SC**H**), 3.44 (1H, ddd, *J* 11.2, 9.1, 6.1 Hz) and 3.49 (1H, ddd, *J* 11.2, 8.8, 5.9 Hz, NCH_2CH_2), 3.71 (1H, dd, *J* 11.5, 6.5 Hz) and 3.84 (1H, dd, *J* 11.5, 9.1 Hz, CH_2OH), 4.90 (1H, d, *J* 14.3 Hz) and 5.05 (1H, d, *J* 14.3 Hz, NCH_2Ph), 5.10 (1H, dd, *J* 10.5, 1.8 Hz) and 5.20 (1H, dd, *J* 17.3, 1.8 Hz, CH_2=CH), 5.64 (1H, ddd, *J* 17.3, 10.5, 8.8 Hz, CH_2=CH), 7.28-7.34 (5H, m, Aromatic CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.1 (NCH_2CH_2), 49.3 (CH_2=CHCH)), 51.8 (NCH_2Ph), 52.8 (NCH_2CH_2), 55.1 (C=SCH), 63.0 (CH_2OH), 118.4 (CH_2=CH), 128.1, 128.3, 128.8 (Aromatic CH), 134.9 (Aromatic C), 135.6 (CH_2=CH), 202.7 (C=S); *m*/*z* (CI) 262 (MH^+, 100%), 244 (27), 191 (40), 86 (57). HRMS found 262.1258, $C_{15}H_{20}NOS$ (MH^+) requires 262.1266.

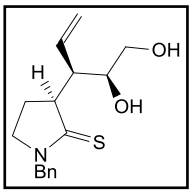
(*R*)-1-Benzyl-3-((*S*)-1-hydroxybut-3-en-2-yl)pyrrolidine-2-thione (245)



To a suspension of silica gel-supported $NaIO_4$ powder (0.32 g) in DCM (1 mL) was added a solution of diol **243** (47.0 mg, 0.16 mmol) in DCM (1 mL) and the mixture stirred for 1 h at rt. After removal of the solid by filtration the DCM was removed by concentratinon *in vacuo* and the intermediate aldehyde was dissolved in an EtOH/THF mixture (2:1, 3 mL) and $NaBH_4$ (60.0 mg, 1.59 mmol) added. The solution was stirred for 15 minutes at rt, then HCl (1 M) was added until neutral. The resulting solution was diluted with H_2O (5 mL), organic material extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by preparative TLC (SiO_2, petrol/EtOAc 1:1) afforded alcohol **245** (13.0 mg, 31%) as a pale yellow oil: $[\alpha]_D^{20}$ +71.4 (*c* 0.28 in $CHCl_3$).

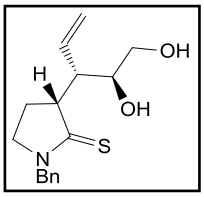
Other spectroscopic data was identical to that for **244**.

(*S*)-1-Benzyl-3-((2*S*,3*R*)-1,2-dihydroxypent-4-en-3-yl)pyrrolidine-2-thione (242)



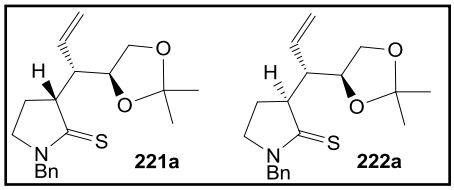
A solution of lactam **220b** (100 mg, 0.19 mmol) in a 1:1 mixture of 60% aq. AcOH (10 mL) and THF (10 mL) was stirred at 50 °C for 24 h. Petrol (30 mL) was added, the aq. layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 40 mL) and toluene (3 × 40 mL) to give diol **242** (52.2 mg, 93%) as a yellow oil, which gave spectroscopic data identical to that of previous samples.

(*R*)-1-Benzyl-3-((2*S*,3*S*)-1,2-dihydroxypent-4-en-3-yl)pyrrolidine-2-thione (243)



A solution of lactam **221b** (6.0 mg, 11.6 μmol) in a 1:1 mixture of 60% aq. AcOH (1 mL) and THF (1 mL) was stirred at 50 °C for 24 h. Petrol (5 mL) was added, the aq. layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 5 mL) and toluene (3 × 5 mL) to give diol **243** (2.30 mg, 67%) as a white solid, which gave spectroscopic data identical to that of previous samples.

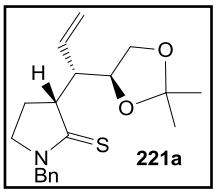
(*R*)-1-Benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (221a) and **(*S*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl) pyrrolidine-2-thione (222a)**



To a solution of bromide **239** (60.0 mg, 0.15 mmol), PPh_3 (3.10 mg, 0.01 mmol), NEt_3 (0.44 g, 0.60 mL, 4.30 mmol) and $Pd(OAc)_2$ (1.3 mg, 4.0 μmol) in DMF (1 mL) was added HCOOH (0.11 mL, 2.92 mmol) and the solution stirred at 65 °C for 6 h. After cooling to rt, the reaction mixture was diluted with brine (10 mL) and the organic material extracted with Et_2O (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded thiolactams **221a** (17.0 mg, 35%) and **222a** (10.0 mg, 21%) as colourless oils:

Spectroscopic data for **221a** and **222a** was identical to those of samples prepared directly from thia-Claisen rearrangement.

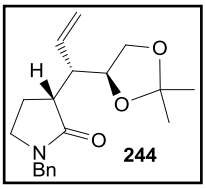
(*R*)-1-Benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (221a) and **(*R*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidin-2-one (244)**



221a

To a solution of $Pd(PPh_3)_4$ (2.80 mg, 2.00 μmol) in THF (0.5 mL) was added a solution of bromide **239** (50.0 mg, 0.12 mmol) and $SnBu_3H$ (50.0 μL, 0.19 mmol) in THF (0.5 mL) and the solution heated to reflux for 24 h. The mixture was cooled to rt, diluted with brine (10 mL) and the organic material extracted with DCM (3 × 25 mL). The extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded product **221a** (20.0 mg, 50%) as a colourless oil:

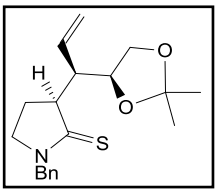
For **221a**, spectroscopic data was identical to that of the sample prepared via thia-Claisen rearrangement.



244

Further elution gave lactam **244** (*ca*. 1.00 mg, *ca*. 3%) as a pale yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2922, 2853, 1682; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.33 (3H, s) and 1.35 (3H, s, $C(CH_3)_2$), 1.82 (1H, m, NCH_2CHH), 2.03 (1H, m, NCH_2CHH), 2.32 (1H, dt, *J* 10.0, 2.5 Hz, CH_2=CHC**H**), 3.04 (1H, m, C=OC**H**), 3.13 (2H, dd, *J* 8.3, 5.7 Hz, NCH_2CH_2), 3.58 (1H, dd, *J* 8.3, 6.7 Hz, OC**H**H), 3.96 (1H, dd, *J* 8.3, 6.1 Hz, OCH**H**), 4.35 (1H, d, *J* 14.8 Hz, NC**H**HPh), 4.45 (1H, d, *J* 14.8 Hz, NCH**H**Ph), 4.74 (1H, dt, *J* 12.6, 6.1 Hz, OC**H**), 5.13 (1H, dd, *J* 10.2, 1.8 Hz, C**H**H=CH), 5.51 (1H, dd, *J* 17.1, 1.8 Hz CH**H**=CH), 5.96 (1H, dt, *J* 17.1, 10.2 Hz, CH_2=C**H**), 7.19-7.31 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.4 (NCH_2CH_2), 25.7 and 27.0 ($C(CH_3)_2$), 41.5 (C=O**C**H), 45.0 (NCH_2CH_2), 46.5 (NCH_2Ph), 51.3 (CH_2=CH**C**H), 68.6 (OCH_2), 75.2 (O**C**H), 109.2 (**C**Me_2), 119.8 (**C**H_2=CH), 127.5, 128.1, 128.6 (Aromatic **C**H), 134.6 (CH_2=**C**H), 136.7 (Aromatic **C**), 174.8 (**C**=O); *m/z* (CI) 316 (MH^+, 42%), 286 (30), 258 (100), 215 (30), 175 (32), 111 (33), 91 (45), 74 (42). HRMS found 316.1916, $C_{19}H_{26}NO_3$ (MH^+) requires 316.1913.

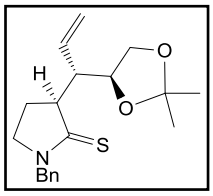
(*S*)-1-Benzyl-3-((*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (220a)



To a solution of $Pd(PPh_3)_4$ (0.50 mg, 0.43 μmol) in THF (0.2 mL) was added a solution of bromide **238** (9.00 mg, 22.0 μmol), and $SnBu_3H$ (9.00 μL, 33.5 μmol) in THF (0.3 mL) and the solution heated to reflux overnight. The mixture was cooled to rt, diluted with brine (5 mL) and organic material extracted with DCM (3 × 10 mL). The extracts were washed with brine (10 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by preparative TLC (SiO_2, petrol/EtOAc 9:1 (× 3 runs)) afforded product **220a** (4.00 mg, 60%) as a pale yellow oil:

Spectroscopic data of **220a** is identical to that of the sample prepared via thia-Claisen rearrangement.

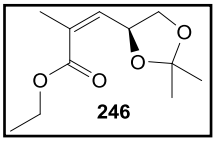
(*S*)-1-Benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (222a)



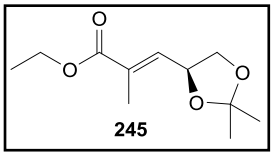
To a solution of $Pd(PPh_3)_4$ (700 μg, 48.0 μmol) in THF (0.15 mL) was added a solution of bromide **240** (10.0 mg, 24.0 μmol) and $SnBu_3H$ (12.0 μL, 0.05 mmol) in THF (0.15 mL) and the solution heated to reflux for 24 h. The mixture was cooled to rt, diluted with brine (3 mL) and the organic material extracted with DCM (3 × 10 mL). The extracts were washed with brine (5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded product **222a** (*ca*. 3.90 mg, 49%) as a colourless oil.

Spectroscopic data for **222a** is identical to that of the sample prepared via thia-Claisen rearrangement.

(*S*,*Z*)-Ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylacrylate (246) and (*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylacrylate (245)

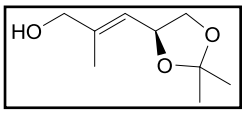


To a solution of diol **210** (2.00 g, 7.63 mmol) in 5% aq. $NaHCO_3$ (10 mL) was added a solution of $NaIO_4$ (1.99 g, 9.30 mmol) in H_2O (15 mL) dropwise and the resulting solution stirred for 1 h. Ethyl 2-(diethoxyphosphoryl)propanoate (4.50 mL, 20.5 mmol) and K_2CO_3 (6 M, 35 mL) were added successively and the solution stirred at rt for 5 d. H_2O was added to dissolve the solid present and the organic material was extracted with DCM (3 × 40 mL), washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol→petrol/Et_2O 19:1) afforded *Z*-ester **246** (695 mg, 21%) as a colourless oil: $[\alpha]_D^{20}$ = –45.9 (*c* 0.41 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 2986, 1714, 1652; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.32 (3H, t, *J* 7.1 Hz, $CH_2C\mathbf{H}_3$), 1.40 (3H, s) and 1.47 (3H, s, $C(C\mathbf{H}_3)_2$), 1.94 (3H, s, $C(C\mathbf{H}_3)$), 3.62 (1H, dd, *J* 8.0, 6.9 Hz, OC**H**HCH), 4.21 (2H, q, *J* 7.1 Hz, $C\mathbf{H}_2CH_3$), 4.32 (1H, dd, *J* 8.0, 6.7 Hz, OCH**H**CH), 5.28 (1H, app. q, *J* 6.9 Hz, OC**H**), 6.09 (1H, dd, *J* 6.8, 1.5 Hz, CMe=C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.3 ($CH_2\mathbf{C}H_3$), 20.1 ($C(\mathbf{C}H_3)$), 25.5 and 26.7 ($C(\mathbf{C}H_3)_2$), 60.7 ($\mathbf{C}H_2CH_3$), 69.6 ($O\mathbf{C}H_2CH$), 74.0 (O**C**H), 109.4 ($\mathbf{C}Me_2$), 129.4 (**C**Me=CH), 142.3 (CMe=**C**H), 167.0 (**C**=O); *m*/*z* (CI) 215 (MH^+, 9%), 199 (30), 181 (40), 169 (32), 157 (100); HRMS found 215.1278, $C_{11}H_{19}O_4$ (MH^+) requires 215.1283.



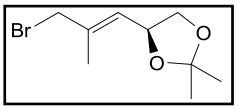
Further elution (SiO_2, petrol/Et_2O 19:1→85:15) afforded *E*-ester **245** (1.09 g, 33%) as a colourless oil: $[\alpha]_D^{20}$ = +13.0 (*c* 0.49 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 2986, 1714; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.31 (3H, t, *J* 7.2 Hz, $CH_2C\mathbf{H}_3$), 1.43 (3H, s) and 1.47 (3H, s, $C(C\mathbf{H}_3)_2$), 1.91 (3H, d, *J* 1.3 Hz, $C(C\mathbf{H}_3)$), 3.65 (1H, t, *J* 7.9 Hz) and 4.18 (1H, dd, *J* 8.3, 6.2 Hz, $OC\mathbf{H}_2CH$), 4.19-4.26 (2H, m, $OC\mathbf{H}_2CH_3$), 4.88 (1H, td, *J* 8.0, 6.2 Hz, OC**H**), 6.70 (1H, dq, *J* 8.3, 1.5 Hz, CMe=C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.1 ($C(\mathbf{C}H_3)$, 14.3 ($CH_2\mathbf{C}H_3$), 25.9 and 26.7 ($C(\mathbf{C}H_3)_2$), 61.0 ($\mathbf{C}H_2CH_3$), 68.7 ($O\mathbf{C}H_2CH$), 72.8 (O**C**H), 109.8 ($\mathbf{C}Me_2$), 131.1 (**C**Me=CH), 138.0 (CMe=**C**H), 167.4 (**C**=O); *m*/*z* (CI) 215 (MH^+, 15%), 197 (20), 181 (23), 169 (26), 143 (34), 141 (100); HRMS found 215.1285, $C_{11}H_{19}O_4$ (MH^+) requires 215.1283.

(*S*,*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol (247)



To a solution of ester **245** (846 mg, 3.95 mmol) in DCM (20 mL) at –78 °C was added DIBAL (1.0 M in hexane, 8.40 mL, 8.40 mmol) dropwise, and the resulting mixture stirred for 1 h at –78 °C. MeOH (40 mL) and Et_2O (30 mL) were added and the solution stirred at –78 °C for 30 mins. After this time period, the solution was warmed to rt and aq. sat. Rochelle's salt (40 mL) was added, and the solution stirred for 1 h. The aqueous phase was diluted with H_2O (50 mL), and the organic material was extracted with EtOAc (4 × 50 mL), washed with brine (50 mL) dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3) afforded alcohol **247** (510 mg, 75%) as a colourless oil: $[\alpha]_D^{21}$ = +11.3 (*c* 0.36 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 3408 br, 2987, 2933, 2873, 1681; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.42 (3H, s) and 1.45 (3H, s, C(C**H**$_3$)$_2$), 1.76 (3H, s, C(C**H**$_3$)), 3.57 (1H, t, *J* 8.0 Hz, OC**H**HCH), 4.06 (2H, s, C**H**$_2$OH), 4.11 (1H, dd, *J* 8.0, 6.0 Hz, OCH**H**CH), 4.85 (1H, td, *J* 8.4, 6.0 Hz, OC**H**), 5.50 (1H, dq, *J* 8.6, 1.5 Hz, CMe=C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1 (C**C**H$_3$), 26.0 and 26.8 (C(**C**H$_3$)$_2$), 67.7 (**C**H$_2$OH), 69.4 (O**C**H$_2$CH), 72.4 (O**C**H), 109.1 (**C**Me$_2$), 121.9 (CMe=**C**H), 141.1 (**C**Me=CH);

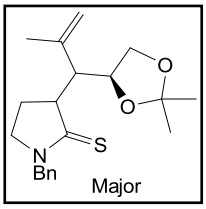
(*S*,*E*)-4-(3-Bromo-2-methylprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (248)



To a stirred solution of alcohol **247** (408 mg, 2.37 mmol) in DCM (20 mL) at 0 °C was added triphenylphosphine (684 mg, 2.61 mmol), followed by *N*-bromsuccinimide (443 mg, 2.49 mmol) portionwise over a few minutes and the solution stirred at rt for 2 h 10 mins. The reaction was quenched with H_2O (15 mL) and the organic material extracted with DCM (3 × 30 mL), washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 4:1) afforded bromide **248** (450 mg, 81%) as a pale yellow oil: $[\alpha]_D^{21}$ = +19.7 (*c* 0.59 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 2986, 2937, 2873; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (3H, s) and 1.44 (3H, s, C(C**H**$_3$)$_2$), 1.87 (3H, d, *J* 1.2 Hz, C(C**H**$_3$)=CH), 3.57 (1H, t, *J* 8.0 Hz, OC**H**H), 3.94 (1H, d, *J* 9.8 Hz) and 3.97 (1H, d, *J* 9.8 Hz, BrC**H**$_2$), 4.11 (1H, dd, *J* 8.0, 6.1 Hz, OCH**H**), 4.77 (1H, dt, *J* 8.0, 6.1 Hz, OC**H**), 5.63 (1H, d, *J* 8.4 Hz, CMe=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3 (C(**C**H$_3$)=CH), 25.9 and 26.7 (C(**C**H$_3$)$_2$), 39.6 (Br**C**H$_2$), 69.0 (O**C**H$_2$), 72.7 (O**C**H),

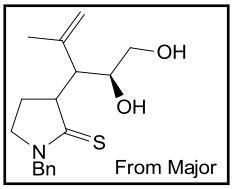
109.3 (**C**Me_2), 128.1 (CMe=**C**H), 137.1 (**C**Me=CH); *m*/*z* (CI) 235/237 (MH^+, 19/19%), 128 (100); HRMS found 235.0343, $C_9H_{16}{}^{79}BrO_2$ (MH^+) requires 235.0334.

1-Benzyl-3-(1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylallyl)pyrrolidine-2-thione (249)



A mixture of thioamide **219** (225 mg, 1.18 mmol), bromide **248** (305 mg, 1.30 mmol) and 4Å molecular sieves (300 mg) in MeCN (3 mL) was stirred under an argon atmosphere for 5 d; further MeCN was added (6 mL) and the mixture warmed to 40 °C. Triethylamine (181 µL, 1.29 mmol) was added and the resulting solution stirred at 40 °C for 8 h. The mixture was cooled to rt, diluted with DCM (100 mL), washed with 2% citric acid (2 × 150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 19:1→47:3) afforded thiolactam **249** (167 mg, 41%) as a white solid; mpt. 53-54 °C: $[\alpha]_D^{22}$ = +34.6 (*c* 0.34 in $CHCl_3$); υ_{max}/cm^{-1} (solid) 2985, 2932, 2877, 1643, 1508, 1453; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.31 (3H, s) and 1.36 (3H, s, C(C**H**$_3$)$_2$), 1.82 (3H, s, C(C**H**$_3$)=CH_2), 2.14-2.20 (2H, m, NBnCH_2C**H**$_2$), 3.19 (1H, t, *J* 1.9 Hz, C=SC**H**), 3.28 (1H, dd, *J* 10.6, 1.9 Hz, OCHC**H**), 3.49 (1H, m, NBnC**H**H), 3.62 (1H, dd, *J* 8.3, 7.3 Hz, OC**H**H), 3.64 (1H, m, NBnCH**H**), 4.06 (1H, dd, *J* 8.3, 6.0 Hz, OCH**H**), 4.49 (1H, ddd, *J* 10.6, 7.3, 6.0 Hz, OC**H**), 4.82 (2H, m, C(CH_3)=C**H**$_2$), 4.91 (1H, d, *J* 14.6 Hz) and 5.07 (1H, d, *J* 14.6 Hz, NC**H**$_2$Ph), 7.29-7.36 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.0 (NBnCH_2**C**H_2), 23.0 (C(**C**H_3)=CH_2), 26.0 and 26.6 (C(**C**H_3)$_2$), 51.9 (N**C**H_2Ph), 52.5 (OCH**C**H), 52.8 (NBn**C**H_2), 56.0 (C=S**C**H), 69.2 (O**C**H_2), 75.0 (O**C**H), 109.5 (**C**Me_2), 113.0 (CMe=**C**H_2), 127.8, 128.3 and 128.7 (Aromatic **C**H), 135.3 (Aromatic **C**), 144.9 (**C**Me=CH_2), 204.7 (**C**=S); *m*/*z* (EI) 345 (M^+, 13%), 330 (14), 244 (76), 229 (35), 191 (100); HRMS found 345.1763, $C_{20}H_{27}O_2NS$ (M^+) requires 345.1757.

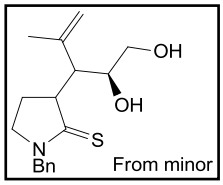
1-Benzyl-3-((2*S*)-1,2-dihydroxy-4-methylpent-4-en-3-yl)pyrrolidine-2-thione (251)



A solution of acetonide **249** (16.0 mg, 46.4 µmol) in 60% aq. AcOH/THF (2:1, 1.5 mL) was heated to 40 ºC and stirred for 18 h. Petrol (5 mL) was added, the aq. layer separated and concentrated *in*

vacuo. The residue was dried by azeotroping successively with EtOH (3 × 5 mL) and toluene (3 × 5 mL). Purification by preparative TLC (SiO_2, petrol/EtOAc 1:1 (× 3 runs)) afforded diol **251** (12.0 mg, 86%) as a cloudy oil: υ_{max}/cm^{-1} (DCM cast) 3396 br, 2921, 2876, 1643, 1509, 1452; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.71 (3H, s, C**H**$_3$), 2.03, (1H, dtd, *J* 12.6, 8.8, 6.1 Hz, NCH$_2$C**H**H), 2.18 (1H, ddt, *J* 12.6, 9.1, 6.0 Hz, NCH$_2$CH**H**), 2.18-2.29 (1H, br s, one of O**H**), 2.92 (1H, dd, *J* 11.0, 3.9 Hz, OCHC**H**), 3.40 (1H, ddd, *J* 9.1, 6.1, 3.9 Hz, C**H**C=S), 3.48 (1H, ddd, *J* 14.7, 8.8, 6.0 Hz, NC**H**HCH$_2$), 3.49 (1H, dd, *J* 11.1, 3.0 Hz, OC**H**H), 3.57 (1H, ddd, *J* 14.7, 8.8, 6.0 Hz, NCH**H**CH$_2$), 3.68-3.77 (2H, m, OCH**H** and one of O**H**), 4.23 (1H, ddd, *J* 11.0, 7.1, 3.0 Hz, OC**H**), 4.87 (2H, m, C**H**$_2$=CMe), 4.97 (1H, d, *J* 14.6 Hz) and 5.03 (1H, d, *J* 14.6 Hz, NC**H**$_2$Ph), 7.31-7.39 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.7 (**C**H$_3$), 23.3 (NCH$_2$**C**H$_2$), 51.4 (OCH**C**H), 52.1 (N**C**H$_2$Ph), 52.9 (N**C**H$_2$CH$_2$), 54.9 (**C**HC=S), 65.4 (O**C**H$_2$), 71.5 (O**C**H), 114.9 (**C**H$_2$=CMe), 128.2, 128.5 and 128.9 (Aromatic **C**H), 134.6 and 143.8 (Aromatic **C** and CH$_2$=**C**Me), 203.4 (**C**=S); *m*/*z* (EI) 305 (M^+, 7%), 274 (11), 272 (19), 245 (16), 244 (100); HRMS found 305.1446, $C_{17}H_{23}O_2NS$ (M^+) requires 305.1444.

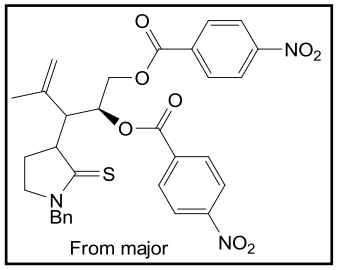
1-Benzyl-3-((2*S*)-1,2-dihydroxy-4-methylpent-4-en-3-yl)pyrrolidine-2-thione (253)



A solution of impure acetonide **250** (6.00 mg, 17.4 μmol) in 60% aq. AcOH/THF (2:1, 1.5 mL) was heated to 40 ºC and stirred for 18 h. Petrol (5 mL) was added, the aq. layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 5 mL) and toluene (3 × 5 mL). Purification by preparative TLC (SiO_2, petrol/EtOAc 1:1 (× 3 runs)) afforded diol **253** (2.00 mg, 38%) as a white feathery solid: mpt. 42-45 °C; υ_{max}/cm^{-1} (solid) 3398 br, 2924, 2879, 1642, 1506, 1452; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.87 (3H, s, C**H**$_3$), 2.01 (1H, dddd, *J* 12.8, 9.3, 9.1, 8.3 Hz, NCH$_2$C**H**H), 2.25 (1H, dddd, *J* 12.8, 9.0, 8.3, 3.8 Hz, NCH$_2$CH**H**), 2.56-2.66 (2H, br m, 2 × O**H**), 3.12 (1H, td, *J* 9.2, 3.0 Hz, C=SC**H**), 3.19 (1H, dd, *J* 7.9, 3.0 Hz, OCHC**H**), 3.47 (1H, dt, *J* 11.1, 8.3 Hz, NC**H**HCH$_2$), 3.57 (1H, *J* 11.1, 9.1, 3.8 Hz, NCH**H**CH$_2$), 3.55 (1H, dd, *J* 12.2, 4.8 Hz, OC**H**H), 3.64-3.71 (1H, br m, OCH**H**), 4.01 (1H, m, OC**H**), 4.97 (1H, d, *J* 14.2 Hz, NC**H**HPh), 5.01 (2H, m, C**H**$_2$=CMe), 5.10 (1H, d, *J* 14.2 Hz, NCH**H**Ph), 7.31-7.40 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ; 23.2 (NCH$_2$**C**H$_2$), 23.4 (C**H**$_3$), 49.5

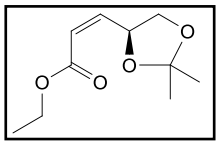
(OCH**C**H), 52.1 ($NCH_2\mathbf{C}H_2$), 52.3 ($N\mathbf{C}H_2Ph$), 56.6 (C=S**C**H), 63.9 ($O\mathbf{C}H_2$), 70.6 (O**C**H), 114.7 ($\mathbf{C}H_2$=CMe), 128.3, 128.5 and 129.0 (Aromatic **C**H), 134.7 and 145.1 (Aromatic **C** and CH_2=**C**Me), 203.6 (**C**=S); *m*/*z* (EI) 305 (M^+, 4%), 274 (6), 272 (10), 245 (19), 244 (100); HRMS found 305.1446, $C_{17}H_{23}O_2NS$ (M^+) requires 305.1444.

(2*S*)-3-(1-Benzyl-2-sulfanylidenepyrrolidin-3-yl)-4-methyl-2-[(4-nitrophenyl) carbonyloxy]pent-4-en-1-yl 4-nitrobenzoate (252)



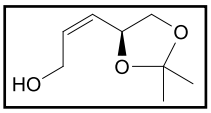
To a solution of diol **251** (22.0 mg, 0.07 mmol) in DCM (1 mL) at 0 ºC was added *para*-nitrobenzoyl chloride (40.0 mg, 0.22 mmol), NEt_3 (50.0 µL, 0.36 mmol) and DMAP (5 mg, mmol) and the mixture stirred at rt for 18 h. The reaction was quenched by the addition of H_2O (1 mL) and the organic material extracted into DCM (3 × 3 mL), washed with brine (2 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by preparative TLC (SiO_2, petrol/EtOAc 3:2) gave thiolactam **252** (22.0 mg, 51%) as a white solid: mpt. 136-138 ºC; $[\alpha]_D^{22}$ = +23.0 (*c* 0.1 in $CHCl_3$); υ_{max}/cm^{-1} (solid) 2921, 2851, 1724, 1606, 1526, 1453, 1347; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.87-1.95 (1H, m, $NBnCH_2C\mathbf{H}H$), 1.92 (3H, s, $C\mathbf{H}_3$), 2.21 (1H, m, $NBnCH_2CH\mathbf{H}$), 3.03 (1H, td, *J* 9.7, 1.9 Hz, C**H**C=S), 3.24 (1H, t, *J* 11.1, 2.7 Hz) and 3.36 (1H, dt, *J* 11.1, 8.6 Hz, $NBnC\mathbf{H}_2$), 3.78 (1H, d, *J* 14.2 Hz, NC**H**HPh), 4.21 (1H, dd, *J* 11.7, 1.9 Hz, OCHC**H**), 4.41 (1H, dd, *J* 12.3, 5.7 Hz) and 4.84 (1H, dd, *J* 12.3, 2.4 Hz, OCH**H**), 5.07 (1H, s) and 5.01 (1H, s, $C\mathbf{H}_2$=C), 5.27 (1H, d, *J* 14.2 Hz, NCH**H**Ph), 5.86 (1H, ddd, *J* 11.7, 5.6, 2.2 Hz, OC**H**), 7.02 (2H, d, *J* 8.2 Hz), 7.17-7.21 (3H, m) and 8.19-8.32 (8H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.2 ($NBnCH_2\mathbf{C}H_2$), 22.9 ($\mathbf{C}H_3$), 46.9 (OCH**C**H), 51.8 ($NBn\mathbf{C}H_2$), 52.0 ($N\mathbf{C}H_2Ph$), 55.8 (**C**HC=S), 65.5 ($O\mathbf{C}H_2$), 72.0 (O**C**H), 114.9 ($\mathbf{C}H_2$=C), 123.8 and 123.8 (Aromatic **C**H), 128.2 (Aromatic **C**), 128.4, 128.8, 131.0 and 131.4 (Aromatic **C**H), 134.5 ($NCH_2\mathbf{C}$), 135.1 (Aromatic **C**), 143.6 (CH_2=**C**), 150.8 and 151.1 (Aromatic **C**), 164.3 (CHO**C**=O), 164.5 ($CH_2O\mathbf{C}$=O), 203.7 (**C**=S); *m*/*z* (CI) 604 (MH^+, 100%), 437 (53), 288 (100); HRMS found 604.1747, $C_{31}H_{30}O_8N_3S$ (MH^+) requires 604.1754

(*S*,*Z*)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (257)[78,79]



To a solution of diacetonide **210** (4.70 g, 17.9 mmol) suspended in 4:1 MeOH/H_2O (90 mL) was added $NaHCO_3$ (4.47 g, 53.2 mmol) and the solution cooled to 0 °C. To this, a solution of $NaIO_4$ (5.43 g, 25.0 mmol) in MeOH/H_2O (1:1 v/v, 30 mL) was added dropwise and the reaction stirred for 2 h at rt. After cooling to –60 °C, PPh_3CHCO_2Et (15.0 g, 43.1 mmol) was added dropwise and the solution stirred for 2 h at –60 °C, and then overnight at 0 °C. To this solution, DCM (100 mL) was added and the Ph_3PO precipitate removed by filtration. The organic material was extracted with DCM (3 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 97:3) gave ester **257** (2.92 g, 41%) as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2986, 2938, 1716, 1644; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (3H, t, *J* 7.1 Hz, C**H**$_3$CH$_2$), 1.39 (3H, s) and 1.45 (3H, s, C(C**H**$_3$)$_2$), 3.61 (1H, dd, *J* 8.3, 6.8 Hz, OC**H**H), 4.15-4.17 (2H, m, CH$_3$C**H**$_2$), 4.38 (1H, dd, *J* 8.3, 7.0 Hz, OCH**H**), 5.49 (1H, m, OC**H**), 5.84 (1H, dd, *J* 11.7, 1.7 Hz, C=OC**H**), 6.35 (1H, dd, *J* 11.7, 6.7 Hz, C=OCH=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) 14.3 (**C**H$_3$CH$_2$), 25.5 and 26.6 (C(**C**H$_3$)$_2$), 60.5 (CH$_3$**C**H$_2$), 69.5 (O**C**H$_2$), 73.6 (O**C**H), 109.8 (**C**Me$_2$), 120.9 (C=O**C**H), 149.3 (C=OCH=**C**H), 165.7 (**C**=O); *m*/*z* (CI) 201 (MH^+, 7%), 183 (16), 156 (19), 145 (19), 144 (100). HRMS found 201.1128, $C_{10}H_{17}O_4$ (MH^+) requires 201.1127.

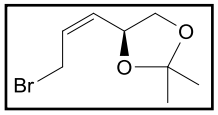
(*S*,*Z*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (258)[70]



To a solution of ester **257** (2.46 g, 12.3 mmol) in DCM (40 mL) at –78 °C was added DIBAL (1.2 M in toluene, 25.5 mL, 30.7 mmol) dropwise, and the solution stirred for 2 h at –78 °C. After warming the reaction mixture to rt, MeOH (80 mL), Et_2O (100 mL) and aq. sat. Rochelle's salt (100 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (60 mL), organic material extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 4:1→7:3) afforded title alcohol **258** (1.73 g, 89%) as a colourless liquid: $[\alpha]_D^{20}$ +12.8 (*c* 1.08 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 3395, 2987, 2936, 2873, 1647; ^1H NMR ($CDCl_3$, 500 MHz) δ

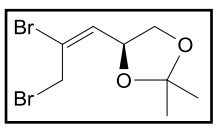
1.39 (3H, s) and 1.42 (3H, s, C(C**H**$_3$)$_2$), 3.57 (1H, t, *J* 7.8 Hz) and 4.09 (1H, dd, *J* 8.2, 6.2 Hz, OC**H**$_2$), 4.21 (1H, ddd, *J* 13.1, 6.0, 1.1 Hz) and 4.30 (1H, ddd, *J* 13.1, 7.1, 1.3 Hz, C**H**$_2$OH), 4.85 (1H, m, OC**H**), 5.56 (1H, m, HOCH$_2$CH=C**H**), 5.83 (1H, m, HOCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 125 MHz) 26.0 and 26.8 (C(**C**H$_3$)$_2$), 58.7 (**C**H$_2$OH), 69.6 (O**C**H$_2$), 72.0 (O**C**H), 109.5 (**C**Me$_2$), 129.7 (HOCH$_2$CH=**C**H), 133.2 (HOCH$_2$**C**H=CH).

(*S*,*Z*)-4-(3-Bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (259)[70]



To a stirred solution of alcohol **258** (1.61 g, 10.2 mmol) in DCM (70 mL) at 0 °C was added triphenylphosphine (2.94 g, 11.2 mmol), followed by *N*-bromosuccinimide (1.90 g, 10.6 mmol) portionwise over a few minutes. After stirring the solution at rt for 3 h, H_2O (80 mL) was added and the organic material extracted with DCM (3 × 80 mL). The combined extracts were washed with brine (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 85:15) afforded bromide **259** (1.63 g, 72%) as a colourless oil: $[\alpha]_D^{20}$ –146.9 (*c* 0.98 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2986, 2936, 2873, 1056; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (3H, s), 1.43 (3H, s, C(C**H**$_3$)$_2$), 3.59 (1H, t, *J* 7.2 Hz, OC**H**H), 3.98 (1H, dd, *J* 10.4, 7.9 Hz, C**H**HBr), 4.08 (1H, t, *J* 10.4 Hz, CH**H**Br), 4.16 (1H, dd, *J* 8.2, 6.2 Hz, OCH**H**), 4.89 (1H, m, OC**H**), 5.59 (1H, dd, *J* 10.8, 8.3 Hz, BrCH$_2$CH=C**H**), 5.92 (1H, m, BrCH$_2$C**H**=CH); ^{13}C NMR ($CDCl_3$, 125 MHz); 25.9 and 26.0 (**C**H$_3$CCH$_3$ and **C**H$_2$Br), 26.7 (CH$_3$C**C**H$_3$), 69.2 (O**C**H$_2$), 71.3 (O**C**H), 109.8 (**C**Me$_2$), 129.4 (BrCH$_2$**C**H=CH), 132.3 (BrCH$_2$CH=**C**H); *m*/*z* (CI) 221 (MH^+, 6%), 142 (83), 112 (32), 84 (100). HRMS found 221.0181, $C_8H_{14}{}^{79}BrO_2$ (MH^+) requires 221.0177.

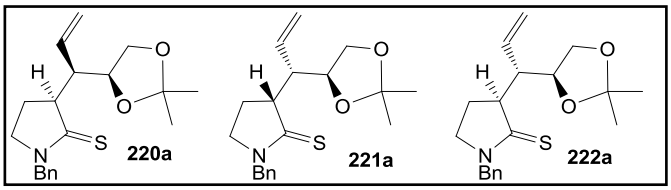
(*S*,*E*)-4-(2,3-Dibromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (260)



To a stirred solution of alcohol **230** (0.43 g, 1.82 mmol) in DCM (20 mL) at 0 °C was added triphenylphosphine (0.52 g, 1.98 mmol), followed by *N*-bromosuccinimide (0.34 g, 1.91 mmol) portionwise over a few minutes and the solution was stirred at rt for 24 h. The reaction was quenched with H_2O (30 mL), organic material extracted with DCM (3 × 30 mL), washed with brine (50 mL),

dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 97:3) afforded bromide **260** (0.29 g, 54%) as a colourless oil: $[\alpha]_D^{20}$ –4.0 (*c* 0.43 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2986, 2933, 2873, 1638; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37 (3H, s) and 1.41 (3H, s, (C**H**$_3$)$_2$), 3.65 (1H, dd, *J* 8.5, 7.0 Hz) and 4.15 (1H, dd, *J* 8.5, 6.2 Hz, OC**H**$_2$), 4.19 (1H, d, *J* 11.4 Hz) and 4.42 (1H, d, *J* 11.4 Hz, C**H**$_2$Br), 4.71 (1H, ddd, *J* 8.3, 7.0, 6.2 Hz, OC**H**) 6.04 (1H, d, *J* 8.3 Hz, C(Br)=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) 25.7 and 26.6 (C(**C**H$_3$)$_2$), 32.2 (**C**H$_2$Br), 68.5 (O**C**H$_2$), 72.7 (O**C**H), 110.1 (**C**Me$_2$), 124.2 (Br**C**=CH) 134.8 (BrC=**C**H); *m*/*z* (CI) 299/301/303 (MH^+, 17/27/15%), 283/285/287 (26/48/25), 241/243/245 (50/95/45), 227/229/231 (63/100/47). HRMS found 298.9279, $C_8H_{13}{}^{79}Br_2O_2$ (MH^+) requires 298.9282.

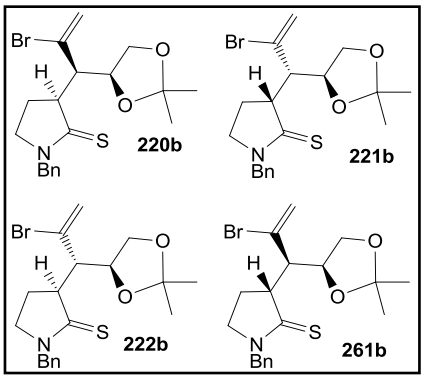
(*S*)-1-Benzyl-3-((*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (220a), **(*R*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (221a)** and **(*S*)-1-benzyl-3-((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl) pyrrolidine-2-thione (222a)**



A mixture of thioamide **219** (0.24 g, 1.26 mmol), *Z*-bromide **259** (0.30 g, 1.36 mmol) and 4Å molecular sieves (0.30 g) in MeCN (2 mL) was stirred under an argon atmosphere for 3 d. Further MeCN (6 mL) was added and the mixture warmed to 35 °C. Triethylamine (0.19 mL, 1.36 mmol) was added and the resulting solution stirred at 35 °C for 7 h. The mixture was cooled to rt, diluted with DCM (30 mL), washed with 2% citric acid (2 × 70 mL), dried ($MgSO_4$) and concentrated *in* vacuo. Purification by flash chromatography (SiO_2, petrol/EtOAc 24:1→4:1) afforded thiolactam products **220a** (42.1 mg, 10%), **221a** (46.1 mg, 11%) and **222a** (75.0 mg, 18%), all as pale yellow oils:

For **220a**, **221a** and **222a**, the spectroscopic data was identical to that for material previously obtained.

(*S*)-1-Benzyl-3-((*R*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (220b), **(*R*)-1-benzyl-3-((*S*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (221b)**, **(*S*)-1-benzyl-3-((*S*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (222b)** and **(*R*)-1-benzyl-3-((*R*)-2-bromo-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)pyrrolidine-2-thione (261b)**



A mixture of thioamide **209** (73.0 mg, 0.38 mmol), *E*-bromide **260** (125 mg, 0.42 mmol) and 4Å molecular sieves (125 mg) in MeCN (1 mL) was stirred under an argon atmosphere for 4 d. Further MeCN was added (2 mL) and the mixture warmed to 35 °C. Triethylamine (59.0 μL, 0.42 mmol) was added and the resulting solution stirred at 35 °C for 8 h. The mixture was cooled to rt, diluted with DCM (20 mL), washed with 2% citric acid (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 99:1→9:1) afforded thiolactams **220b** (*ca*. 1.60 mg, *ca*. 1%) as a pale yellow oil, **221b** (9.00 mg, 6%) as a colourless oil, **222b** (56.1 mg, 39%) as a colourless oil and **261b** (*ca*.14.0 mg, *ca*. 9%) as a yellow oil:

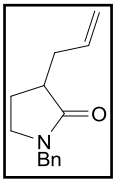
For **220b**, **221b** and **222b**: Spectroscopic data was identical to that of previously prepared samples.

For **261b**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (3H, s) and 1.47 (3H, s, C(C**H**$_3$)$_2$), 2.00-2.48 (2H, m, NCH$_2$C**H**$_2$), 2.97 (1H, m), 3.52 (1H, m) and 3.65-3.71 (2H, m, C=SC**H**, CH$_2$=CBrC**H** and NC**H**$_2$CH$_2$), 3.87 (1H, dd, *J* 8.0, 7.6 Hz) and 4.14 (1H, dd, *J* 8.0, 5.8 Hz, OC**H**$_2$), 4.49 (1H, m, OC**H**), 4.92 (1H, d, *J* 14.3 Hz) and 5.08 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 5.61 (1H, d, *J* 1.4 Hz) and 5.98 (1H, d, *J* 1.4 Hz, C**H**$_2$=CHBr), 7.30-7.36 (5H, m, Aromatic C**H**).

APPROACHES TOWARDS THE SARAIN CORE

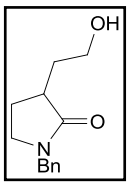
Ring expansion method

3-Allyl-1-benzylpyrrolidin-2-one (271)[80]



To a solution of diisopropylamine (8.50 mL, 60.2 mmol) in THF (200 mL) at −78 ºC was added ^{n}BuLi (2.5 M in hexanes, 25.6 mL, 64.0 mmol) and the solution stirred for 15 min. To this was added a solution of lactam **102** (10.0 g, 57.1 mmol) in THF (50 mL) dropwise and the solution stirred at −78 ºC for 30 min. Allyl bromide (5.00 mL, 57.8 mmol) was then added and the solution warmed to rt and stirred for 18 h. H_2O (75 mL) was added and the organic material extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:4→3:7) afforded alkene **271** (10.5 g, 86%) as a colourless oil: υ_{max}/cm^{-1} (neat) 3030, 2975, 2915, 1678; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.72 (1H, m) and 2.14 (1H, m, NBnCH$_2$C**H**$_2$), 2.22 (1H, m, C**H**HCH=CH$_2$), 2.55-2.62 (1H, dtd, *J* 12.3, 8.7, 4.1 Hz, C**H**C=O), 2.63-2.68 (1H, m, CH**H**CH=CH$_2$), 3.19 (2H, dd, *J* 8.3, 5.7 Hz, NBnC**H**$_2$), 4.44 (1H, d, *J* 14.6 Hz) and 4.50 (1H, d, *J* 14.6 Hz, NC**H**$_2$Bn), 5.07 (1H, app. d, *J* 10.1 Hz) and 5.11 (1H, app. d, *J* 17.1, Hz, CH=C**H**$_2$), 5.80 (1H, ddt, *J* 17.1, 10.1, 6.9 Hz, C**H**=CH$_2$), 7.22-7.25 (2H, m) , 7.30 (1H, m) and 7.32-7.36 (2H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.9 (NBnCH$_2$**C**H$_2$), 35.5 and 41.4 (**C**H$_2$CH=CH$_2$ and **C**HC=O), 44.8 (NBn**C**H$_2$), 46.7 (N**C**H$_2$Ph), 116.9 (CH=**C**H$_2$), 127.5, 128.1 and 128.7 (Aromatic **C**H), 135.6 (**C**H=CH$_2$), 136.6 (Aromatic **C**), 176.0 (**C**=O).

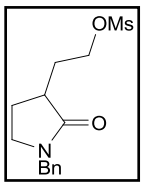
1-Benzyl-3-(2-hydroxyethyl)pyrrolidin-2-one (272)[80]



An ozone enriched stream of oxygen was bubbled through a solution of alkene **271** (9.80 g, 45.6 mmol) in MeOH (250 mL) until a blue colour persisted. After this time, oxygen was bubbled through the solution until the blue colour dissipated. $NaBH_4$ (17.2 g, 455 mmol) was added in 10 portions over 1 h and the solution stirred for a further 1 h. The reaction was quenched with H_2O (100 mL) and 2 M HCl (50 mL) and the organic material extracted with EtOAc (3 × 200 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:1 EtOAc) afforded alcohol **272** (8.40, 79%) as a

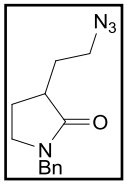
colourless oil: υ_{max}/cm^{-1} (neat) 3398 br, 2938, 2870, 1658; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.82 (2H, m, NBnCH$_2$C**H**H and C**H**HCH$_2$OH), 1.93 (1H, m, CH**H**CH$_2$OH), 2.23 (1H, m, NBnCH$_2$CH**H**), 2.68 (1H, qd, *J* 9.3, 4.7 Hz, C**H**C=O), 3.26 (2H, dd, *J* 8.9, 5.0 Hz, NBnC**H**$_2$), 3.76-3.90 (2H, m, C**H**$_2$OH), 4.45 (1H, d, *J* 14.8 Hz) and 4.49 (1H, d, *J* 14.8 Hz, NC**H**$_2$Ph), 7.21-7.40 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.9 (NBnCH$_2$**C**H$_2$), 34.7 (**C**H$_2$CH$_2$OH), 42.4 (**C**HC=O), 45.5 (NBn**C**H$_2$), 47.0 (N**C**H$_2$Ph), 62.1 (**C**H$_2$OH), 127.7, 128.1 and 128.8 (Aromatic **C**H), 136.1 (Aromatic **C**), 177.5 (**C**=O).

2-(1-Benzyl-2-oxopyrrolidin-3-yl)ethyl methanesulfonate (273)[80]



To a solution of alcohol **272** (4.96 g, 21.3 mmol) in DCM (150 mL) at 0 ºC was added NEt_3 (6.30 mL, 45.2 mmol), followed by MsCl (3.60 mL, 46.5 mmol) and the mixture stirred at 0 ºC for 2.5 h. H_2O (50 mL) was added and the organic material extracted with DCM (3 × 100 mL), washed with brine (50 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to give crude mesylate **273** (8.04 g, 121%) as a colourless oil, which was used without further purification: υ_{max}/cm^{-1} (neat) 3029, 2934, 1671; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65-1.75 (1H, m, NBnCH$_2$C**H**H), 1.89 (1H, m, C**H**HCH$_2$OMs), 2.25-2.36 (2H, m, NBnCH$_2$CH**H** and CH**H**CH$_2$OMs), 2.63 (1H, m, C**H**C=O), 3.05 (3H, s, C**H**$_3$), 3.22 (2H, dd, *J* 8.8, 5.0 Hz, NBnC**H**$_2$), 4.39-4.52 (4H, m, NBnC**H**$_2$ and C**H**$_2$OMs), 7.21-7.38 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (NBnCH$_2$**C**H$_2$), 31.2 (**C**H$_2$CH$_2$OMs), 37.3 (SO$_2$**C**H$_3$), 38.5 (**C**HC=O), 44.8 (NBn**C**H$_2$), 46.8 (N**C**H$_2$Ph), 68.3 (**C**H$_2$OMs), 127.7, 128.1 and 128.8 (Aromatic **C**H), 136.3 (Aromatic **C**), 175.4 (**C**=O).

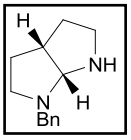
3-(2-Azidoethyl)-1-benzylpyrrolidin-2-one (274)[80]



To a solution of crude mesylate **273** (8.04 g, *ca*. 25.0 mmol) in DMSO (60 mL) was added NaN_3 (5.48 g, 84.3 mmol) and the solution stirred at 60 ºC for 2 h. The reaction was quenched by the addition of H_2O and the organic material was extracted into EtOAc (3 × 150 mL), washed with brine (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:1) gave azide **274** (4.90 g, 89% from alcohol **272**) as a colourless oil:

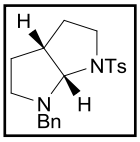
υ_{max}/cm^{-1} (neat) 2934, 2872, 2091, 1676; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.65-1.72 (2H, m, C**H**HCH$_2$N$_3$ and NBnCH$_2$C**H**H), 2.18-2.27 (2H, m, CH**H**CH$_2$N$_3$ and NBnCH$_2$CH**H**), 2.58 (1H, dtd, *J* 9.2, 8.8, 5.5 Hz, C**H**C=O), 3.21 (2H, dd, *J* 8.7, 5.1 Hz, NBnC**H**$_2$), 3.49 (2H, m, C**H**$_2$N$_3$), 4.46 (1H, d, *J* 14.7 Hz) and 4.48 (1H, *J* 14.7 Hz, NC**H**$_2$Ph), 7.21-7.36 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.2 (NBnCH$_2$**C**H$_2$), 30.8 (**C**H$_2$CH$_2$N$_3$), 39.5 (**C**HC=O), 44.8 (NBn**C**H$_2$), 46.8 (N**C**H$_2$Ph), 49.6 (**C**H$_2$N$_3$), 127.6, 128.1 and 128.7 (Aromatic **C**H), 136.4 (Aromatic **C**), 175.7 (**C**=O).

1-Benzyl-octahydropyrrolo[2,3-b]pyrrole (275)[80]



To a solution of azide **274** (396 mg, 1.53 mmol) in THF (25 mL) was added PBu$_3$ (0.95 mL, 3.80 mmol) and the solution stirred at rt for 30 min. After this time, LiAlH$_4$ (1 M in THF, 0.95 mL, 0.95 mmol) was added dropwise and the solution stirred for 50 min. Sat. aq. Rochelle's salt (1 M, 16 mL) was added and the mixture stirred for 1 h. The organic material was extracted into EtOAc (3 × 100 mL), washed with brine (100 mL), dried (MgSO$_4$) and solvent removed *in vacuo*. Purification by flash chromatography (Al$_2$O$_3$, petrol/EtOAc 1:19→3:17) gave amine **275** (233 mg, 71%) as a yellow oil: υ_{max}/cm^{-1} (neat) 3289 br, 2956, 2866, 2793, 1653, 1603; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.42 (1H, m, NHCH$_2$C**H**H), 1.51 (1H, m) and 1.73 (1H, m, NBnCH$_2$C**H**$_2$), 1.95 (1H, m, NHCH$_2$CH**H**), 2.00-2.30 (1H, br s, N**H**), 2.34 (1H, td, *J* 8.8, 6.3 Hz, NHC**H**H), 2.59-2.67 (1H, m, C**H**CHNBn), 2.80 (1H, ddd, *J* 8.8, 6.7, 3.7 Hz, NHCH**H**), 2.82-3.00 (2H, m, NBnC**H**$_2$), 3.65 (1H, d, *J* 13.1 Hz) and 3.83 (1H, d, *J* 13.1 Hz, NC**H**$_2$Ph), 4.12 (1H, app. d, *J* 7.7 Hz, NC**H**N), 7.20-7.37 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 30.8 (NBnCH$_2$**C**H$_2$), 33.7 (NHCH$_2$**C**H$_2$), 41.5 (**C**HCHNBn), 45.0, 52.0 and 57.3 (NBnC**H**$_2$, NHC**H**$_2$ and NC**H**$_2$Ph), 83.2 (N**C**HN), 126.9, 128.3 and 129.0 (Aromatic **C**H), 139.4 (Aromatic **C**).

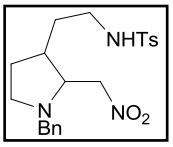
1-Benzyl-6-tosyl-octahydropyrrolo[2,3-b]pyrrole (276)[80]



To a solution of amine **275** (97.0 mg, 0.48 mmol) in DCM (4 mL) was added NEt$_3$ (0.15 mL, 1.09 mmol) dropwise, followed by TsCl (0.20 g, 1.05 mmol) and the solution stirred at rt for 2 h. After the addition of H$_2$O (5 mL), the

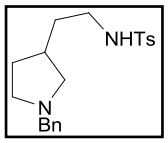
organic material was extracted into EtOAc (3 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, DCM/MeOH 1:99→1:49) gave bicycle **276** (144 mg, 85%) as a pale yellow solid: mpt. 84-86 °C; υ_{max}/cm^{-1} (solid) 2968, 2868, 2781, 1598; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.31 (1H, m, $NTsCH_2CHH$), 1.35-1.50 (2H, m, $NTsCH_2CH$**H** and $NBnCH_2CHH$), 1.85-2.00 (1H, m, $NBnCH_2CH$**H**), 2.40-2.52 (1H, m, NBnC**H**H), 2.41 (3H, s, CH_3), 2.55-2.71 (2H, m, C**H**CHNBn and NBnC**H**H), 3.31 (1H, m) and 3.62 (1H, dd, *J* 12.5, 7.8 Hz, $NTsCH_2$), 4.00 (1H, d, *J* 13.6 Hz) and 4.06 (1H, d, *J* 13.6 Hz, NCH_2Ph), 5.08 (1H, app. d, *J* 6.7 Hz, NC**H**N), 7.20-7.40 (7H, m, Aromatic C**H**), 7.77 (2H, d, *J* 8.2 Hz, SO_2CCH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 (CH_3), 29.9 and 32.4 ($NBnCH_2CH_2$ and CHCHNBn), 41.9 (CH_2CH_2NTs), 48.1 and 50.5 ($NBnCH_2$ and $NTsCH_2$), 55.4 (NCH_2Ph), 84.8 (NCHCN), 126.7, 127.2, 128.1, 128.8 and 129.7 (Aromatic CH), 137.3 (NCH_2C), 139.3 ($SO_2CCHCHC$), 143.2 (SO_2C).

N-(2-(1-Benzyl-2-(nitromethyl)pyrrolidin-3-yl)ethyl)-4-methylbenzenesulfonamide (279)



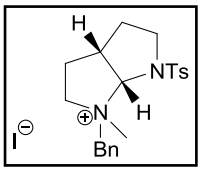
Bicycle **276** (4.0 mg, 0.01 mmol) was stirred in $MeNO_2$ at rt under argon for 18 h. After this time the solvent was removed *in vacuo* to give amine **279** (4.3 mg, 92%) as an orange solid: mpt. 50-54 °C; υ_{max}/cm^{-1} (solid) 3287 br, 2929, 2806, 1598, 1547; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.42 (1H, m, $NBnCH_2CHH$), 1.50 (1H, m) and 1.60 (1H, m, $NHTsCH_2CH_2$), 1.90 (1H, m, $NBnCH_2CH$**H**), 2.11 (1H, m, NBnCHC**H**), 2.38-2.46 (1H, m, NBnC**H**H), 2.45 (3H, s, $PhCH_3$), 2.90 (1H, m, NBnCH**H**), 2.93-3.01 (3H, m, CH_2NHTs and NBnC**H**), 3.50 (1H, d, *J* 12.9 Hz) and 3.92 (1H, d, *J* 12.9 Hz, CH_2Ph), 4.35 (2H, m, CH_2NO_2), 4.53 (1H, br s, N**H**), 7.24-7.40 (5H, m, Aromatic C**H**), 7.34 (2H, d, *J* 8.4 Hz, SO_2CCHCH), 7.74 (2H, app. d, *J* 8.4 Hz, SO_2CCH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 ($PhCH_3$), 28.8 ($NBnCH_2CH_2$), 34.4 (CH_2CH_2NHTs), 39.5 (NCHCH), 41.4 ($NHTsCH_2$), 52.0 ($NBnCH_2$), 59.2 (NCH_2Ph), 67.3 (NBnCH), 78.2 (CH_2NO_2), 127.1, 127.4, 128.5, 128.8 and 129.8 (Aromatic CH), 136.7 (SO_2C), 138.4 (NCH_2C), 143.6 ($SO_2CCHCHC$); *m/z* (ES+) 416 ($[M–H]^+$, 100%); HRMS found 416.1631, $C_{21}H_{26}N_3O_4S$ ($[M–H]^+$) requires 416.1644.

***N*-(2-(1-Benzylpyrrolidin-3-yl)ethyl)-4-methylbenzenesulfonamide (280)**



To a solution of bicycle **276** (10.0 mg, 28.1 μmol) in THF/EtOH (3:2, 7 mL) was added Pd-C (1.5 mg) under an argon atmosphere. The mixture was evacuated of air and then H_2 was added; this was repeated another 2 times and the solution stirred for at rt for 18 h. After this time, the flask was flushed with argon, the product filtered through Celite® and solvent removed to give amine **280** (9.9 mg, 98%) as a yellow oil: υ_{max}/cm^{-1} (neat) 3276 br, 2925, 2790, 1599; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.40 (1H, m, NBnCH$_2$C**H**H), 1.52-1.63 (2H, m, NHTsCH$_2$C**H**$_2$), 1.96 (1H, m, NBnCH$_2$CH**H**), 2.26 (1H, m, NBnCH$_2$C**H**), 2.31 (1H, m, *J* 9.4, 5.9 Hz, NBnC**H**HCH), 2.42 (3H, s, PhC**H**$_3$), 2.56 (1H, m) and 2.63 (1H, m, NBnC**H**$_2$), 2.70 (1H, dd, *J* 9.4, 7.6 Hz, NBnCH**H**CH), 2.88 (1H, dt, *J* 12.8, 7.1 Hz) and 2.94 (1H, ddd, *J* 12.8, 7.1, 6.0 Hz, C**H**$_2$NHTs), 3.61 (1H, d, *J* 12.7 Hz) and 3.70 (1H, d, *J* 12.7 Hz, NC**H**$_2$Ph), 7.26-7.37 (7H, Aromatic C**H** and SO$_2$CCHC**H**), 7.69 (2H, d, *J* 8.2 Hz, SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5 (Ph**C**H$_3$), 29.1 (NBnCH$_2$C**H**$_2$), 34.5 (NHTsCH$_2$**C**H$_2$), 34.5 (NBnCH$_2$**C**H), 41.3 (**C**H$_2$NHTs), 53.4 (NBn**C**H$_2$), 59.7 (NBnC**H**$_2$CH), 60.3 (N**C**H$_2$Ph), 127.0, 127.4, 128.4, 129.3 and 129.7 (Aromatic **C**H), 137.0 and 137.7 (SO$_2$**C** and NCH$_2$**C**), 143.2 (SO$_2$CCHCH**C**); *m*/*z* (FAB) 359 (MH^+, 45%), 286 (39), 176 (100); HRMS found 359.1792, $C_{20}H_{27}N_2O_2S$ (MH^+) requires 359.1793.

1-Benzyl-6-methanesulfonyl-1-methyl-octahydropyrrolo[2,3-b]pyrrol-1-ium iodide (281)

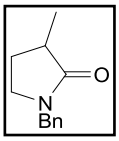


Bicycle **276** (37.0 mg, 0.10 mmol) was stirred with iodomethane (64.3 μL, 1.03 mmol) at rt under argon. After this time, the excess iodomethane was removed *in vacuo*. Purification by flash chromatography (SiO_2, DCM/MeOH 9:1) gave salt **281** (42.0 mg, 81%) as a yellow solid: mpt. 100-102 °C; υ_{max}/cm^{-1} (solid) 2957, 1596; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (2H, m, NTsCH$_2$C**H**$_2$), 1.80 (1H, m, NBnCH$_2$C**H**H), 2.45 (3H, s, PhC**H**$_3$), 2.62 (1H, m, NBnCH$_2$CH**H**), 2.91 (3H, s, NC**H**$_3$), 3.08 (1H, ddd, *J* 11.5, 6.3, 3.7 Hz, NBnC**H**H), 3.55 (1H, ddd, *J* 11.8, 6.9, 5.5 Hz) and 3.69 (1H, dt, *J* 11.8, 7.5 Hz, NTsC**H**$_2$), 3.88 (1H, m, NCHC**H**), 4.64 (1H, ddd, *J* 11.5, 6.9, 3.1 Hz, NBnCH**H**), 4.86 (1H, d, *J* 13.0 Hz) and 5.71 (1H, d, *J* 13.0 Hz, NC**H**$_2$Ph), 6.39 (1H, d, *J* 8.3 Hz, NC**H**N),

7.43-7.56 (5H, m, Aromatic C**H**), 7.64 (2H, m, SO_2CCHC**H**), 7.92 (2H, d, *J* 8.4 Hz, SO_2CC**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (Ph**C**H_3), 27.4 (NBnCH_2**C**H_2), 30.1 (NTsCH_2**C**H_2), 43.2 (NCH**C**H), 43.8 (N**C**H_3), 51.0 (NTs**C**H_2), 62.0 (NBn**C**H_2), 66.5 (N**C**H_2Ph), 95.5 (N**C**HN), 128.0, 128.0, 129.4, 130.8, 132.7 and 132.8 (Aromatic **C**H and Aromatic **C**), 145.7 (SO_2CCHCH**C**); *m*/*z* (ES+) 371 ($[M–I]^+$, 100%), 150 (28); HRMS found 371.1782, $C_{21}H_{27}N_2O_2S$ ($[M–I]^+$) requires 371.1793.

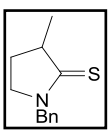
Acid catalysed rearrangement method

1-Benzyl-3-methylpyrrolidin-2-one (291)[28]



To a solution of 1-benzyl-2-pyrrolidinone (**102**, 16.5 mL, 86.4 mmol) in THF (250 mL) at −78 °C was added ^{n}BuLi (2.5 M in hexanes, 41.0 mL, 104 mmol) dropwise and the mixture stirred for 30 min. MeI (10.8 mL, 173 mmol) was then added very slowly and the solution stirred for 30 min at −78 °C, followed by a further 1 h at rt. The reaction mixture was quenched by the addition of $NH4^+Cl^–$ (100 mL) and the organic material extracted into EtOAc (3 × 250 mL), washed with brine (200 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3→2:3) gave lactam **291** (15.8 g, 95%) as a yellow oil: υ_{max}/cm^{-1} (neat) 2964, 2931, 2872, 1678; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (3H, d, *J* 7.0 Hz, C**H**$_3$), 1.55-1.65 (1H, m) and 2.22 (1H, m, NBnCH_2C**H**$_2$), 2.52 (1H, m, C**H**), 3.13-3.22 (2H, m, NBnC**H**$_2$), 4.44 (1H, d, *J* 14.7 Hz) and 4.49 (1H, d, *J* 14.7 Hz, NC**H**$_2$Ph), 7.20-7.37 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.6 (**C**H_3), 27.2 (NBnCH_2**C**H_2), 36.9 (**C**H), 44.8 (NBn**C**H_2), 46.9 (N**C**H_2Ph), 127.6, 128.2 and 128.8 (Aromatic **C**H), 136.8 (Aromatic **C**), 177.5 (**C**=O).

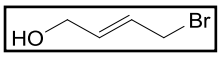
1-Benzyl-3-methylpyrrolidine-2-thione (101)[28]



To a solution of lactam **291** (17.0 g, 89.9 mmol) in THF (400 mL) was added Lawesson's reagent (21.8 g, 49.4 mmol) and the resulting mixture stirred at 40 °C for 2 h. After cooling to rt, H_2O (100 mL) was added and the organic material extracted into EtOAc (3 × 150 mL), washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, 1:19

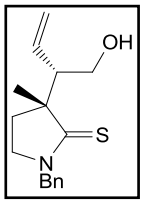
1:9) gave thiolactam **101** (17.0 g, 92%) as a pale yellow oil: υ_{max}/cm^{-1} (neat) 2963, 2927, 2870, 1498, 1448; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (3H, d, *J* 7.1 Hz, C**H**$_3$), 1.65 (1H, m) and 2.29 (1H, m, NBnCH$_2$C**H**$_2$), 2.98 (1H, app. sext, *J* 7.4 Hz, C**H**CH$_3$), 3.46-3.55 (2H, m, NBnC**H**$_2$), 4.97 (1H, d, *J* 14.3 Hz) and 5.06 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 7.30-7.38 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.7 (**C**H$_3$), 28.4 (NBnCH$_2$**C**H$_2$), 49.0 (**C**HMe), 52.0 (N**C**H$_2$Ph), 52.0 (NBn**C**H$_2$), 128.1, 128.3 and 128.9 (Aromatic **C**H), 135.3 (Aromatic **C**), 206.8 (**C**=S).

(*E*)-4-Bromobut-2-en-1-ol (100)[28]



To a solution of ethyl-4-bromocrotonate (20.6 g, 107 mmol) in toluene (70 mL) at −78 °C was added DIBAL (1.2 M in toluene, 224 mL, 269 mmol) and the mixture stirred for 1 h. To the reaction was added Et_2O (30 mL), then MeOH (30 mL) and the solution stirred at −78 °C for 1 h. The solution was warmed to 0 °C and aq. sat. Rochelle's salt (50 mL) was added and the resulting solution stirred at rt for 1 h. The organic material was extracted into Et_2O (3 × 150 mL), washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 4:1→1:1) gave volatile bromide **100** (11.2 g, 77%) as a orange oil: υ_{max}/cm^{-1} (neat) 3296 br, 2934, 2858, 1667; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (1H, br s, O**H**), 3.98 (2H, app. d, *J* 6.3 Hz, C**H**$_2$Br), 4.20 (2H, app. d, *J* 3.5 Hz, C**H**$_2$OH), 5.90-6.02 (2H, m, C**H**CH$_2$OH and C**H**CH$_2$Br); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 32.1 (**C**H$_2$Br), 62.6 (**C**H$_2$OH), 127.5 (**C**HCH$_2$Br), 134.1 (**C**HCH$_2$OH).

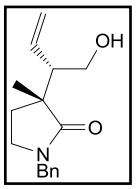
(±)-(*R*)-1-Benzyl-3-((*S*)-1-hydroxybut-3-en-2-yl)-3-methylpyrrolidine-2-thione (99)[28]



A solution of thiolactam **101** (6.30 g, 30.7 mmol) and bromide **100** (5.19 g, 34.6 mmol) in MeCN (4.6 mL) was stirred at rt for 4 d. The solution was diluted with MeCN (160 mL), heated to 40 °C and NEt_3 (4.70 mL, 33.7 mmol) was added; the resulting mixture was stirred for 6.5 h. The mixture was cooled to rt, diluted with DCM (200 mL), washed with 10% citric acid (100 mL) and organic layer collected. Further organic material was extracted from the aqueous layer (2 × 200 mL) and these extracts washed with 10% citric acid (100 mL). The

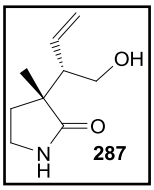
combined organic material was washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→7:3) gave thiolactam **99** (6.80 g, 80%) as a pale yellow solid: mpt. 59-51 °C; υ_{max}/cm^{-1} (solid) 3330 br, 2971, 2956, 2876, 1668, 1503, 1450; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (3H, s, C**H**$_3$), 1.73 (1H, ddd, *J* 12.9, 7.9, 4.5 Hz) and 2.19 (1H, ddd, *J* 12.9, 9.4, 7.8 Hz, NBnCH$_2$C**H**$_2$), 2.96 (1H, dt, *J* 9.9, 6.7 Hz, C**H**CH$_2$OH), 3.40-3.53 (2H, m, NBnC**H**$_2$), 3.58-3.68 (2H, m, C**H**$_2$OH), 5.00 (1H, d, *J* 14.3 Hz) and 5.05 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 5.26-5.32 (2H, m, CH=C**H**$_2$), 5.60-5.70 (1H, dt, *J* 17.0, 9.9 Hz, C**H**=CH$_2$), 7.28-7.38 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.2 (**C**H$_3$), 28.6 (NBnCH$_2$**C**H$_2$), 51.1 and 52.1 (N**C**H$_2$Ph and NBn**C**H$_2$), 54.6 (**C**HCH$_2$OH), 56.7 (**C**Me), 63.2 (**C**H$_2$OH), 120.3 (CH=**C**H$_2$), 128.3, 128.4 and 129.0 (Aromatic **C**H), 135.1 (Aromatic **C**), 135.5 (**C**H=CH$_2$), 208.7 (**C**=S).

(±)-(*R*)-1-Benzyl-3-((*S*)-1-hydroxybut-3-en-2-yl)-3-methylpyrrolidin-2-one (286)[28]

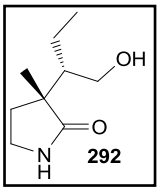


To a solution of thiolactam **99** (11.5g, 41.8 mmol) in DCM (500 mL) at 0 °C was added *m*CPBA (22.4 g, 135 mmol) in 0.25 equivalent portions every 10 min. After this addition, the mixture was stirred for a further 1 h at 0 °C. The solution was warmed to rt, poured into sat. $NaHCO_3$ (200 mL) and organic material collected. Further extraction of the organic material with DCM (2 × 200 mL) followed by drying ($MgSO_4$) and concentration *in vacuo* gave the crude material. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:1 → EtOAc) gave alcohol **286** (9.53 g, 88%) as a yellow solid: mpt. 54-55 °C; υ_{max}/cm^{-1} (solid) 3363 br, 2923, 2861, 1670; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (3H, s, C**H**$_3$), 1.64 (1H, ddd, *J* 12.9, 7.9, 3.6 Hz) and 2.16 (1H, ddd, *J* 12.9, 9.2, 8.0 Hz, NBnCH$_2$C**H**$_2$), 2.29 (1H, m, C**H**CH$_2$OH), 3.14-3.25 (2H, m, NBnC**H**$_2$), 3.66 (1H, dd, *J* 11.3, 4.5 Hz) and 3.94 (1H, dd, *J* 11.3, 4.3 Hz, C**H**$_2$OH), 4.42 (1H, d, *J* 14.7 Hz) and 4.48 (1H, d, *J* 14.7 Hz, NC**H**$_2$Ph), 5.17-5.25 (2H, m, CH=C**H**$_2$), 5.80 (1H, dt, *J* 16.9, 10.1 Hz, C**H**=CH$_2$), 7.20-7.39 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.9 (**C**H$_3$), 29.9 (NBnCH$_2$**C**H$_2$), 44.2 (NBn**C**H$_2$), 47.0 (**C**Me), 47.1 (N**C**H$_2$Ph), 53.2 (**C**HCH$_2$OH), 63.1 (**C**H$_2$OH), 119.4 (CH=**C**H$_2$), 127.8, 128.2 and 128.9 (Aromatic **C**H), 136.1 (Aromatic **C**), 136.2 (**C**H=CH$_2$), 179.0 (**C**=O).

(±)-(*R*)-3-((*S*)-1-Hydroxybut-3-en-2-yl)-3-methylpyrrolidin-2-one (287) and **(±)-(*R*)-3-((*S*)-1-hydroxybutan-2-yl)-3-methylpyrrolidin-2-one (292)**

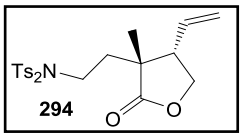


To liquid ammonia at −78 °C was added a solution of alcohol **286** (1.03 g, 3.97 mmol) in THF (60 mL) and the mixture stirred for 15 min. Na pieces were added (183 mg, 7.95 mmol) and the solution stirred for a further 10 min. The reaction was quenched by the addition of $NH_4^+Cl^-$ (50 mL) and was left to stir at 20 °C overnight. The THF was removed *in vacuo* and the organic material extracted with EtOAc (5 × 70 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to afford alcohol **287** (545 mg, 81%) as a white solid: mpt. 74-77 °C; υ_{max}/cm^{-1} (solid) 3251 br, 2961, 2926, 2873, 1677; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.27 (3H, s, C**H**$_3$), 1.79 (1H, dddd, *J* 12.9, 7.9, 3.3, 0.6 Hz, C**H**HCH$_2$NH), 2.28 (1H, dt, *J* 10.1, 4.8 Hz, C**H**CH$_2$OH), 2.32 (1H, ddd, *J* 12.9, 9.1, 7.9 Hz, CH**H**CH$_2$NH), 3.31-3.42 (2H, m, C**H**$_2$NH), 3.65 (1H, m, C**H**HOH), 3.78 (1H, br s, O**H**), 3.90 (1H, dd, *J* 11.2, 4.8 Hz, CH**H**OH), 5.22 (1H, dd, *J* 17.0, 1.9 Hz) and 5.27 (1H, dd, *J* 10.1, 1.9 Hz, CH=C**H**$_2$), 5.83 (1H, dt, *J* 17.0, 10.1 Hz, C**H**=CH$_2$), 6.30 (1H, br s, N**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.6 (**C**H$_3$), 32.3 (**C**H$_2$CH$_2$NH), 39.7 (**C**H$_2$NH), 45.6 (**C**CH$_3$), 52.7 (**C**HCH$_2$OH), 63.0 (**C**H$_2$OH), 119.4 (CH=**C**H$_2$), 136.0 (**C**H=CH$_2$), 182.6 (**C**=O); *m*/*z* (FAB) 192 (MNa$^+$, 100%), 176 (23); HRMS found 192.0997, $C_9H_{15}NO_2Na$ (MNa$^+$) requires 192.1000.

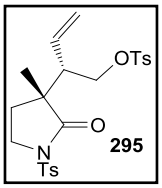


When excess Na was used (5 equiv.) and the reaction stirred for longer than 10 mins, alcohol **287** was isolated as a white solid along with alcohol **292**: mpt. 69-70 °C; υ_{max}/cm^{-1} (solid) 3252 br, 2960, 2933, 2877, 1675; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, t, *J* 7.4 Hz, CH$_2$C**H**$_3$), 1.31 (3H, s, CC**H**$_3$), 1.32-1.36 (1H, m, C**H**CH$_2$OH), 1.43 (1H, m) and 1.54 (1H, m, C**H**$_2$CH$_3$), 1.83 (1H, dddd, *J* 13.1, 7.8, 3.1, 0.6 Hz) and 2.26 (1H, dt, *J* 13.1, 8.8 Hz, C**H**$_2$CH$_2$NH), 3.30-3.46 (2H, m, C**H**$_2$NH), 3.68 (1H, m) and 3.86 (1H, d, *J* 11.9 Hz, C**H**$_2$OH), 4.61 (1H, br s, O**H**), 6.52 (1H, br s, N**H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8 (CH$_2$**C**H$_3$), 18.5 (**C**H$_2$CH$_3$), 22.9 (C**C**H$_3$), 33.5 (**C**H$_2$CH$_2$NH), 40.0 (**C**H$_2$NH), 47.5 (**C**CH$_3$), 48.5 (**C**HCH$_2$OH), 59.5 (**C**H$_2$OH), 183.5 (**C**=O); *m*/*z* (CI) 172 (MH$^+$, 100%), 154 (25), 112 (32), 99 (47); HRMS found 172.1334, $C_9H_{18}O_2N$ (MH$^+$) requires 172.1338.

(±)-2-[(3*R*,4*S*)-4-Ethenyl-3-methyl-2-oxooxolan-3-yl]-*N*-[(4-methylbenzene) sulfonyl]-S-(4-methylphenyl)ethane-1-sulfonamido (294) and **(±)-(*S*)-2-((*R*)-3-methyl-2-oxo-1-tosylpyrrolidin-3-yl)but-3-enylmethylbenzenesulfonate (295)**



To a solution of NaH (60% dispersion in mineral oil-washed with hexane, 32.0 mg, *ca*. 0.80 mmol) in THF (3 mL) at 0 °C was added alcohol **287** (50.0 mg, 0.30 mmol) and the solution stirred for 1 h 20 min. TsCl (124 mg, 0.65 mmol) was added and the mixture stirred at rt for 18 h. H_2O (3 mL) was then added slowly and the organic material extracted into DCM (3 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1) gave lactone **294** (58.0 mg, 41%) as a white solid: mpt. 98-100 °C; υ_{max}/cm^{-1} (solid) 2973, 2927, 1763, 1597; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24 (3H, s, C**H**$_3$CC=O), 1.74 (1H, ddd, *J* 13.2, 11.7, 5.4 Hz) and 1.87 (1H, ddd, *J* 13.2, 11.7, 4.9 Hz, C**H**$_2$CH$_2$NTs$_2$), 2.45 (6H, s, 2 × PhC**H**$_3$), 2.85 (1H, br q, *J* 8.7 Hz, C**H**CH$_2$O), 3.73 (1H, m) and 3.80 (1H, m, C**H**$_2$NTs$_2$), 4.01 (1H, t, *J* 9.6 Hz) and 4.32 (1H, dd, *J* 9.3, 7.7 Hz, C**H**$_2$O), 5.19 (1H, dt, *J* 17.0, 1.3 Hz) and 5.26 (1H, ddd, *J* 10.2, 1.3, 0.8 Hz, CH=C**H**$_2$), 5.65 (1H, ddd, *J* 17.0, 10.2, 8.3 Hz, C**H**=CH$_2$), 7.33 (4H, app. d, *J* 8.4 Hz, 2 × SO$_2$CCHC**H**), 7.81 (4H, app. d, *J* 8.4 Hz, 2 × SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.2 (**C**H$_3$CC=O), 21.7 (2 × Ph**C**H$_3$), 31.8 (**C**H$_2$CH$_2$NTs$_2$), 44.0 (CH$_3$**C**C=O), 44.8 (**C**H$_2$NTs$_2$), 51.8 (**C**HCH$_2$O), 68.4 (**C**H$_2$O), 120.3 (CH=**C**H$_2$), 128.4 and 129.8 (Aromatic **C**H), 131.3 (**C**H=CH$_2$), 135.1 (2 × SO$_2$**C**), 145.0 (2 × SO$_2$CCHCH**C**), 179.5 (**C**=O); m/z (ES+) 500 (MNa$^+$, 100%), 306 (27), 180 (27); HRMS found 500.1177, $C_{23}H_{27}NO_6NaS_2$ (MNa$^+$) requires 500.1178.

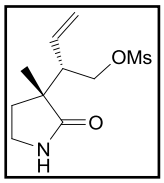


Further elution (SiO_2, petrol/EtOAc 9:1→4:1) afforded tosylate **295** (45.0 mg, 32%) as a pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 2977, 2926, 1728, 1597; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (3H, s, C**H**$_3$CC=O), 1.70 (1H, ddd, *J* 13.2, 7.9, 3.9 Hz) and 2.18 (1H, ddd, *J* 13.2, 8.9, 7.9 Hz, NTsCH$_2$C**H**$_2$), 2.40-2.50 (1H, m, C**H**C=O), 2.45 (3H, s) and 2.46 (3H, s, PhC**H**$_3$), 3.68 (1H, dt, *J* 9.9, 7.9 Hz) and 3.81 (1H, ddd, *J* 9.9, 8.9, 3.9 Hz, NTsC**H**$_2$), 3.97 (1H, dd, *J* 10.2, 7.5 Hz) and 4.08 (1H, dd, *J* 10.2, 4.7 Hz, C**H**$_2$OTs), 5.08 (1H, dd, *J* 16.9, 1.5 Hz) and 5.13 (1H, dd, *J* 10.0, 1.5 Hz, CH=C**H**$_2$), 5.32 (1H, dt, *J* 16.9, 10.0 Hz, C**H**=CH$_2$), 7.31-7.36 (4H, m, 2 × SO$_2$CCHC**H**), 7.72 (2H, app. d, *J* 8.3 Hz) and 7.86 (2H, app. d, *J* 8.4 Hz, 2 ×

$SO_2CC\mathbf{H}$),); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.7 and 21.7 (2 × Ph$\mathbf{C}H_3$), 22.0 ($\mathbf{C}H_3CC=O$), 28.7 ($NTsCH_2\mathbf{C}H_2$), 44.0 ($NTs\mathbf{C}H_2$) 47.0 ($CH_3\mathbf{C}C=O$), 49.3 ($\mathbf{C}HC=O$), 69.5 ($\mathbf{C}H_2OTs$), 121.3 ($CH=\mathbf{C}H_2$), 127.8 and 127.9 (2 × $SO_2C\mathbf{C}H$), 129.7 and 129.9 (2 × $SO_2CCH\mathbf{C}H$), 132.6 ($\mathbf{C}H=CH_2$), 132.7 and 134.6 (2 × $SO_2\mathbf{C}$), 145.0 and 145.4 (2 × $SO_2CCHCH\mathbf{C}$), 176.1 ($\mathbf{C}$=O); *m*/*z* (ES+) 500 (MNa^+, 100%), 369 (32), 306 (50); HRMS found 500.1163, $C_{23}H_{27}NO_6NaS_2$ (MNa^+) requires 500.1178.

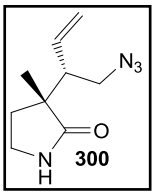
The same mixture of products was obtained when the reaction was attempted with NEt_3 (1.05 equiv.), TsCl (2.1 equiv.), THF at 0 °C to reflux as the first step, followed by NaH (2.1 equiv.) at 0 °C to rt.

(±)-(*S*)-2-((*R*)-3-Methyl-2-oxopyrrolidin-3-yl)but-3-enyl methanesulfonate (296)

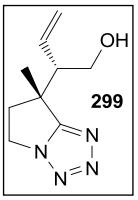


To solution of alcohol **287** (25.0 mg, 0.15 mmol) in DCM (1.7 mL) at 0 °C was added NEt_3 (43.0 µL, 0.31 mmol) followed by MsCl (24.0 µL, 0.31 mmol) and the mixture stirred at rt for 24 h. After adding H_2O to the reaction mixture (1 mL), the organic material was extracted into EtOAc (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 3:7 → EtOAc) gave mesylate **296** (37.1 mg, 82%) as a white solid: mpt. 81-82 °C υ_{max}/cm^{-1} (solid) 3385 br, 3244 br, 2969, 2933, 1688; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.22 (3H, s, $CC\mathbf{H}_3$), 1.80 (1H, ddd, *J* 13.0, 7.8, 3.6 Hz) and 2.23 (1H, ddd, *J* 13.0, 8.9, 7.5 Hz, $C\mathbf{H}_2CH_2NH$), 2.64 (1H, m, $C\mathbf{H}CH_2OMs$), 3.00 (3H, s, $SO_2C\mathbf{H}_3$), 3.29-3.39 (2H, m, $C\mathbf{H}_2NH$), 4.31 (1H, dd, *J* 9.9, 8.6 Hz) and 4.37 (1H, dd, *J* 9.9, 4.6 Hz, $C\mathbf{H}_2OMs$), 5.27 (1H, d, *J* 17.0 Hz) and 5.32 (1H, app. d, *J* 10.0 Hz, $CH=C\mathbf{H}_2$), 5.63 (1H, dt, *J* 17.0, 10.0 Hz, $C\mathbf{H}=CH_2$), 6.64 (1H, br s, N**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.1 ($C\mathbf{C}H_3$), 30.8 ($\mathbf{C}H_2CH_2NH$), 37.3 ($SO_2\mathbf{C}H_3$), 39.0 ($\mathbf{C}H_2NH$), 44.5 ($\mathbf{C}CH_3$), 53.5 ($\mathbf{C}HCH_2OMs$), 69.8 ($\mathbf{C}H_2OMs$), 121.1 ($CH=\mathbf{C}H_2$), 133.7 ($\mathbf{C}H=CH_2$), 181.(**C**=O); *m*/*z* (CI) 248 (MH^+, 55%), 152 (100); HRMS found 248.0957, $C_{10}H_{18}O_4NS$ (MH^+) requires 248.0957.

(±)-(*R*)-3-((*S*)-1-Azidobut-3-en-2-yl)-3-methylpyrrolidin-2-one (300) and **(±)-(*S*)-2-((*R*)-7-methyl-6,7-dihydro-5H-pyrrolo[1,2-e]tetrazol-7-yl)but-3-en-1-ol (299)**

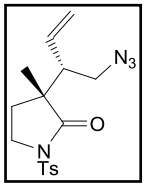


To a solution of NaN_3 (3.00 g, 46.2 mmol) in DMSO (13.7 mL) at 80 °C was added a solution of mesylate **296** (2.29 g, 9.27 mmol) in DMSO (6.4 mL) dropwise. After stirring for 4 h the mixture was cooled to rt and H_2O (10 mL) was added. The organic material was extracted into EtOAc (3 × 20 mL), washed with brine (15 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3→1:1) gave azide **300** (1.31 g, 73%) as a white solid: mpt. 40-41 °C; υ_{max}/cm^{-1} (solid) 3178 br, 3084, 2966, 2924, 2101, 1675; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.19 (3H, s, C**H**$_3$), 1.79 (1H, ddd, *J* 13.1, 8.0, 3.6 Hz) and 2.22 (1H, ddd, *J* 13.1, 8.9, 7.4 Hz, C**H**$_2$CH$_2$NH), 2.53 (1H, td, *J* 9.9, 4.2 Hz, C**H**CH$_2$N$_3$), 3.27-3.37 (3H, m, C**H**HN$_3$ and C**H**$_2$NH), 3.49 (1H, dd, *J* 12.3, 4.3 Hz, CH**H**N$_3$), 5.23-5.33 (2H, m, CH=C**H**$_2$), 5.54 (1H, dt, *J* 16.7, 9.9 Hz, C**H**=CH$_2$), 6.32 (1H, br s, N**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.1 (**C**H$_3$), 30.6 (**C**H$_2$CH$_2$NH), 38.9 (**C**H$_2$NH), 44.7 (**C**CH$_3$), 50.0 (**C**HCH$_2$N$_3$), 51.7 (**C**H$_2$N$_3$), 120.5 (CH=**C**H$_2$), 135.2 (**C**H=CH$_2$), 181.1(**C**=O); *m*/*z* (CI) 195 (MH^+, 100%); HRMS found 195.1241, $C_9H_{15}N_4O$ (MH^+) requires 195.1246.



Further elution provided tetrazole **299** (144 mg, 8%) as a thick colourless oil: υ_{max}/cm^{-1} (DCM cast) 3390 br, 2979, 2932, 2886, 1679, 1640; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.49 (3H, s, C**H**$_3$), 2.10-2.16 (1H, br t, *J* 5.8 Hz, O**H**), 2.55-2.65 (2H, m, NCH$_2$C**H**H and C**H**CH=CH$_2$), 3.13 (1H, dt, *J* 13.6, 7.3 Hz, NCH$_2$CH**H**), 3.80 (2H, br t, *J* 5.5 Hz, C**H**$_2$OH), 4.32 (2H, t, *J* 7.3 Hz, NC**H**$_2$), 5.30 (2H, m, CH=C**H**$_2$), 5.50 (1H, m, C**H**=CH$_2$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.9 (**C**H$_3$), 39.1 (**C**CH$_3$), 40.9 (NCH$_2$**C**H$_2$), 43.8 (N**C**H$_2$), 54.0 (**C**HCH=CH$_2$), 62.3 (**C**H$_2$OH), 121.3 (CH=**C**H$_2$), 134.4 (**C**H=CH$_2$), 166.4 (N**C**N); *m*/*z* (CI) 195 (MH^+, 100%); HRMS found 195.1252, $C_9H_{15}N_4O$ (MH^+) requires 195.1246.

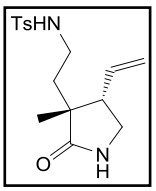
(±)-(*R*)-3-((*S*)-1-Azidobut-3-en-2-yl)-3-methyl-1-tosylpyrrolidin-2-one (288)



A solution of azide **300** (52.0 mg, 0.27 mmol) in THF (2.5 mL) at 0 °C was added to NaH (60% dispersion in mineral oil-washed with hexane, 13.0

mg, *ca*. 0.33 mmol) and the mixture stirred for 1 h. TsCl (61.0 mg, 0.32 mmol) was then added and the resulting solution stirred for 18 h at rt. H_2O (5 mL) was added and the organic material extracted into DCM (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→7:3) gave azide **288** (87.0 mg, 94%) as a cream solid: mpt. 66-68 °C; υ_{max}/cm^{-1} (solid) 2920, 2852, 2097, 1727, 1596; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.08 (3H, s, C**H**$_3$CC=O), 1.73 (1H, ddd, *J* 13.2, 8.2, 4.5 Hz) and 2.16 (1H, ddd, *J* 13.2, 9.0, 7.1 Hz, NCH$_2$C**H**$_2$), 2.44-2.50 (1H, m, C**H**CH$_2$N$_3$), 2.46 (3H, s, PhC**H**$_3$), 3.18 (2H, d, *J* 7.0 Hz, C**H**$_2$N$_3$), 3.79 (1H, ddd, *J* 10.1, 8.2, 7.1 Hz) and 3.83 (1H, ddd, *J* 10.1, 9.0, 4.5 Hz, C**H**$_2$NTs), 5.20 (1H, dd, *J* 17.0, 1.5 Hz) and 5.23 (1H, dd, *J* 10.0, 1.5 Hz, CH=C**H**$_2$), 5.40 (dt, *J* 17.0, 10.0 Hz, C**H**=CH$_2$), 7.36 (2H, d, *J* 8.3 Hz, SO$_2$CCHC**H**), 7.94 (2H, app. d, *J* 8.3 Hz, SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.7 (Ph**C**H$_3$), 23.0 (**C**H$_3$CC=O), 27.6 (NCH$_2$**C**H$_2$), 44.0 (**C**H$_2$NTs), 47.0 (CH$_3$**C**C=O), 49.8 (**C**HCH$_2$N$_3$), 51.4 (**C**H$_2$N$_3$), 121.0 (CH=**C**H$_2$), 128.1 (SO$_2$C**C**H), 129.7 (SO$_2$CCH**C**H), 133.9 (**C**H=CH$_2$), 134.6 (SO$_2$**C**), 145.4 (SO$_2$CCHCH**C**), 176.5 (**C**=O); *m*/*z* (FAB) 371 (MNa$^+$, 100%), 275 (19), 176 (61), 147 (60); HRMS found 371.1147, $C_{16}H_{20}N_4O_3SNa$ (MNa$^+$) requires 371.1154.

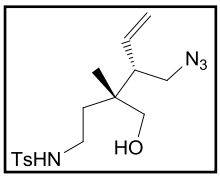
(±)-4-Methyl-*N*-(2-((3*R*,4*S*)-3-methyl-2-oxo-4-vinylpyrrolidin-3-yl)ethyl) benzenesulfonamide (302)



To a solution of azide **288** (15.0 mg, 43.1 μmol) in THF (0.4 mL) was added PBu$_3$ (19.0 μL, 76.1 μmol) and the mixture stirred for 1 h. To this was added benzaldehyde (10.0 μL, 98.1 μmol) and the solution stirred for a further 3 h. The mixture then cooled to 0 °C and a solution of $NaBH_4$ (1.0 mg, 26 μmol) in EtOH (0.5 mL) was added dropwise and the solution stirred for 1 h. H_2O (1 mL) was added and the organic material extracted into DCM (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by preparative TLC (SiO_2, EtOAc) gave lactam **302** (12.2 mg, 90%) as a white solid: mpt. 176-178 °C; υ_{max}/cm^{-1} (solid) 3261 br, 2957, 2925, 2874, 1688, 1599; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.08 (3H, s, C**H**$_3$CC=O), 1.39 (1H, m) and 1.63 (1H, m, C**H**$_2$CH$_2$NHTs), 2.39 (3H, s, PhC**H**$_3$), 2.65 (1H, q, *J* 8.1 Hz, NHCH$_2$C**H**), 2.96-3.08 (2H, dd, *J* 10.0, 8.7 Hz, C**H**$_2$NHTs), 3.15 (1H, ddd, *J* 10.0, 7.7, 1.5 Hz) and 3.37 (1H, dd, *J* 10.0, 8.2 Hz,

NHC**H**$_2$), 5.07 (1H, dt, *J* 17.1, 1.3 Hz) and 5.12 (1H, app. d, *J* 10.3 Hz, CH=C**H**$_2$), 5.65 (1H, m, N**H**Ts), 5.67 (1H, ddd, *J* 17.1, 10.3, 8.3 Hz, C**H**=CH$_2$), 6.03 (1H, br s, N**H**), 7.29 (2H, d, *J* 8.2 Hz, SO$_2$CCHC**H**), 7.72 (2H, d, *J* 8.2 Hz, SO$_2$CC**H**); ^{13}C NMR (CDCl$_3$, 150 MHz) δ 20.5 (**C**H$_3$CC=O), 21.6 (Ph**C**H$_3$), 32.5 (**C**H$_2$CH$_2$NHTs), 39.2 (**C**H$_2$NHTs), 43.8 (NH**C**H$_2$), 45.0 (**C**C=O), 52.0 (NHCH$_2$**C**H), 118.8 (CH=**C**H$_2$), 127.2 (SO$_2$C**C**H), 129.8 (SO$_2$CCH**C**H), 134.0 (**C**H=CH$_2$), 137.4 (SO$_2$**C**), 143.3 (SO$_2$CCHCH**C**), 182.0 (**C**=O); *m*/*z* (CI) 323 (MH$^+$, 29%), 167 (100); HRMS found 323.1424, C$_{16}$H$_{23}$N$_2$O$_3$S (MH$^+$) requires 323.1429.

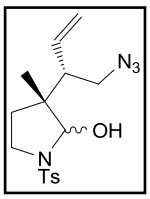
(±)-*N*-((3*R*,4*S*)-4-(Azidomethyl)-3-(hydroxymethyl)-3-methylhex-5-enyl)-4-methylbenzenesulfonamide (306)



To a solution of amide **288** (10.0 mg, 31.0 μmol) in EtOH (0.7 mL) was added NaBH$_4$ (11.0 mg, 290 μmol) and the solution stirred for 5 h. The reaction mixture was neutralised with 1 M HCl and the organic material extracted into EtOAc (3 × 2 mL), washed with brine (5 mL), dried (MgSO$_4$) and solvent removed *in vacuo*. Purification by preparative TLC (SiO$_2$, EtOAc) gave alcohol **306** (2.00 mg, 20%) as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3514 br, 3287 br, 2923, 2851, 2096, 1599; ^{1}H NMR (CDCl$_3$, 600 MHz) δ 0.75 (3H, s, HOCH$_2$CC**H**$_3$), 1.50 (1H, dt, *J* 14.4, 6.9 Hz) and 1.60 (1H, dt, *J* 14.4, 6.9 Hz, C**H**$_2$CH$_2$NHTs), 1.73 (1H, br s, O**H**), 2.26 (1H, td, *J* 9.5, 4.1 Hz, C**H**CH$_2$N$_3$), 2.43 (3H, s, PhC**H**$_3$), 2.99 (2H, q, *J* 6.9 Hz, C**H**$_2$NHTs), 3.15 (1H, dd, *J* 12.4, 9.5 Hz, C**H**HN$_3$), 3.30 (1H, br d, *J* 11.1 Hz, C**H**HOH), 3.37-3.42 (2H, m, CH**H**N$_3$ and CH**H**OH), 4.98 (1H, br t, *J* 6.0 Hz, N**H**Ts), 5.16 (d, *J* 17.0, 1.7 Hz) and 5.22 (1H, dd, *J* 10.0, 1.7 Hz, CH=C**H**$_2$), 5.70 (1H, dt, *J* 17.0, 10.0 Hz, C**H**=CH$_2$), 7.31 (2H, d, *J* 8.3 Hz, SO$_2$CCHC**H**), 7.75 (2H, d, *J* 8.3 Hz, SO$_2$CC**H**); ^{13}C NMR (CDCl$_3$, 150 MHz) δ 19.0 (HOCH$_2$C**C**H$_3$), 21.7 (Ph**C**H$_3$), 35.8 (**C**H$_2$CH$_2$NHTs), 38.8 (**C**H$_2$NHTs), 39.2 (HOCH$_2$**C**CH$_3$), 49.4 (**C**HCH$_2$N$_3$), 51.3 (**C**H$_2$N$_3$), 67.8 (**C**H$_2$OH), 119.6 (CH=**C**H$_2$), 127.2 (SO$_2$C**C**H), 129.9 (SO$_2$CCH**C**H), 136.1 (SO$_2$**C**), 137.0 (**C**H=CH$_2$), 143.6 (SO$_2$CCHCH**C**); *m*/*z* (ES+) 275 (MNa$^+$, 100%), 345 (12), 317 (15); HRMS found 375.1472, C$_{16}$H$_{24}$N$_4$O$_3$NaS (MNa$^+$) requires 375.1467.

Amide **302** (5.00 mg, 50%) was also isolated as a white solid.

(±)-(*R*)-3-((*S*)-1-Azidobut-3-en-2-yl)-3-methyl-1-tosylpyrrolidin-2-ol (304)

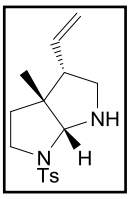


[Major diastereoisomer (MAJ): Minor diastereoisomer (MIN) = 2.9:1]

To a solution of amide **288** (1.94 g, 5.57 mmol) in DCM (50 mL) at −78 °C was added DIBAL (1.2 M in toluene, 5.60 mL, 6.72 mmol) and the mixture stirred for 2.5 h. The reaction was quenched by the addition of Et_2O (20 mL), MeOH (20 mL) and sat. aq. Rochelle's salt (20 mL) and the solution slowly warmed to rt and stirred for 1 h. The organic material was extracted into EtOAc (3 × 100 mL), washed with brine (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to give the crude material. Purification by flash chromatography (SiO_2, petrol/Et_2O 3:2) gave a mixture of diastereoisomers of alcohol **304** (1.85 g, 95%) as a thick pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 3496 br, 2975, 2096, 1598; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.52 (3H, s, NCHCC**H**$_3^{MAJ}$), 1.02 (3H, s, NCHCC**H**$_3^{MIN}$), 1.66 (1H, dd, *J* 12.1, 7.1 Hz, NTsCH$_2$C**H**H^{MAJ}), 1.73-1.83 (2H, m, NTsCH$_2$C**H**H^{MIN}), 1.86 (1H, td, *J* 9.5 4.4 Hz, C**H**CH$_2$N$_3^{MIN}$), 2.06 (1H, m, app. q, *J* 11.4 Hz, NTsCH$_2$CH**H**^{MAJ}), 2.42 (3H, s, PhC**H**$_3^{MAJ}$), 2.44 (3H, s, PhC**H**$_3^{MIN}$), 2.72 (1H, td, *J* 9.3, 4.7 Hz, C**H**CH$_2$N$_3^{MAJ}$), 2.75 (1H, m, O**H**^{MAJ}), 3.12-3.32 (3H, m, NTsC**H**H^{MIN} and C**H**$_2$N$_3^{MIN}$), 3.16 (1H, ddd, *J* 10.6, 9.4, 7.1 Hz, NTsC**H**H^{MAJ}), 3.22 (1H, dd, *J* 12.4, 9.3 Hz) and 3.29 (1H, dd, *J* 12.4, 4.7 Hz, C**H**$_2$N$_3^{MAJ}$), 3.52-3.55 (1H, m, NTsCH**H**^{MIN}), 3.57 (1H, td, *J* 9.4, 0.9 Hz, NTsCH**H**^{MAJ}), 4.78 (1H, ddd, *J* 17.0, 1.5, 0.7 Hz, CH=C**H**H^{MIN}), 4.81 (1H, m, C**H**OH^{MAJ}), 5.03 (1H, d, *J* 2.9 Hz, C**H**OH^{MIN}), 5.12 (1H, dd, *J* 10.2, 1.7 Hz, CH=CH**H**^{MIN}), 5.26 (2H, m, CH=C**H**$_2^{MAJ}$), 5.61 (1H, ddd, *J* 17.0, 10.2, 9.5 Hz C**H**=CH$_2^{MIN}$), 5.78 (1H, ddd, *J* 17.8, 10.0, 9.3 Hz, C**H**=CH$_2^{MAJ}$), 7.30 (2H, dd, *J* 8.6, 0.7 Hz, SO$_2$CCHC**H**^{MAJ}), 7.32 (2H, d, *J* 8.2 Hz, SO$_2$CCHC**H**^{MIN}), 7.73 (2H, m, SO$_2$CC**H**^{MAJ}), 7.74 (2H, m, SO$_2$CC**H**^{MIN}); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.7 (NCHC**C**H$_3^{MIN}$), 16.4 (NCHC**C**H$_3^{MAJ}$), 21.7 (Ph**C**H$_3^{MAJ}$ and Ph**C**H$_3^{MIN}$), 33.9 (NTsCH$_2$**C**H$_2^{MIN}$), 33.9 (NTsCH$_2$**C**H$_2^{MAJ}$), 44.9 (NTs**C**H$_2^{MIN}$), 45.2 (NTs**C**H$_2^{MAJ}$), 46.9 (**C**HCH$_2$N$_3^{MAJ}$), 48.0 (NCH**C**CH$_3^{MIN}$), 48.3 (NCH**C**CH$_3^{MAJ}$), 49.0 (**C**HCH$_2$N$_3^{MIN}$), 51.7 (**C**H$_2$N$_3^{MAJ}$), 51.7 (**C**H$_2$N$_3^{MIN}$), 87.3 (**C**HOH^{MIN}), 89.1 (**C**HOH^{MAJ}), 119.5 (CH=**C**H$_2^{MAJ}$), 120.1 (CH=**C**H$_2^{MIN}$), 127.1 (SO$_2$C**C**H^{MAJ}), 127.2 (SO$_2$C**C**H^{MIN}), 129.9 (SO$_2$CCH**C**H^{MAJ}), 130.0 (SO$_2$CCH**C**H^{MIN}), 135.4 (**C**H=CH$_2^{MIN}$), 135.9 (**C**H=CH$_2^{MAJ}$), 135.9 (SO$_2$**C**^{MAJ}), 136 (SO$_2$**C**^{MIN}), 143.8 (SO$_2$CCHCH**C**^{MAJ}), 144.0 (SO$_2$CCHCH**C**^{MIN});

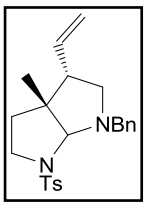
m/*z* (FAB) 373 (MNa^+, 10%), 329 (33), 307 (34), 289 (20), 176 (100); HRMS found 373.1316, $C_{16}H_{22}O_3N_4SNa$ (MNa^+) requires 373.1310.

(±)-(3a*R*,4*S*)-3a-Methyl-1-tosyl-4-vinyl-octahydropyrrolo[2,3-b]pyrrole (303)



To a solution of azide **304** (3.50 g, 10.0 mmol) in THF (100 mL) was added PBu_3 (3.96 mL, 15.0 mmol) and H_2O (270 µL, 15.0 mmol) and the solution stirred for 1 h. After this time, H_2O (50 mL) was added and the THF was removed *in vacuo*. The organic material was extracted into EtOAc (3 × 100mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:1→1:4) gave amine **303** (2.75 g, 90%) as a pale yellow solid: mpt. 45-46 °C; υ_{max}/cm^{-1} (solid) 2955, 2924, 2869, 1640, 1598; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.88 (3H, s, NCHCC**H**$_3$), 1.22 (1H, ddd, *J* 12.6, 6.1, 2.5 Hz) and 1.95 (1H, ddd, *J* 12.6, 10.5, 7.6 Hz,. NTsCH$_2$C**H**$_2$), 2.38 (1H, m, NHCH$_2$C**H**), 2.42 (3H, s, PhC**H**$_3$), 2.88 (1H, ddd, *J* 10.5, 9.5, 6.1 Hz, NTsC**H**H), 3.04 (2H, m, NHC**H**$_2$), 3.50 (1H, ddd, *J* 9.5, 7.6, 2.5 Hz, NTsCH**H**), 4.31 (1H, s, NC**H**N), 5.08 (1H, m) and 5.10 (1H, m, CH=C**H**$_2$), 5.69 (1H, ddd, *J* 17.1, 10.6, 7.6 Hz, C**H**=CH$_2$), 7.32 (2H, d, *J* 8.2 Hz, SO$_2$CCHC**H**), 7.73 (2H, d, *J* 8.2 Hz, SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 (Ph**C**H$_3$), 23.9 (NCHC**C**H$_3$), 31.6 (NTsCH$_2$**C**H$_2$), 47.7 (NTs**C**H$_2$), 48.9 (NH**C**H$_2$), 52.6 (NCH**C**), 53.3 (NHCH$_2$**C**H), 85.3 (N**C**HN), 117.8 (CH=**C**H$_2$), 127.8 (SO$_2$C**C**H), 129.6 (SO$_2$CCH**C**H), 133.5 (SO$_2$**C**), 134.4 (**C**H=CH$_2$), 143.6 (SO$_2$CCHCH**C**); *m*/*z* (ES+) 307 (MH^+, 100%), HRMS found 307.1474, $C_{16}H_{23}N_2O_2S$ (MH^+) requires 307.1480.

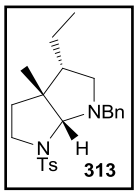
(±)-(3*S*,3a*R*)-1-Benzyl-3a-methyl-6-tosyl-3-vinyl-octahydropyrrolo[2,3-b]pyrrole (289)



To a solution of amine **303** (93.0 mg, 0.30 mmol) in THF (4 mL) at 0 °C was added BnBr (54.0 µL, 0.45 mmol), followed by NEt_3 (47 µL, 0.34 mmol) and the mixture stirred at rt for 18 h. After this time, H_2O was added (2 mL) and the organic material extracted into EtOAc (3 × 5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→4:1) afforded alkene **289** (108 mg, 90%) as a yellow solid:

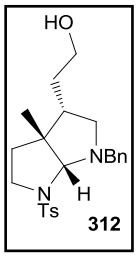
mpt. 46-48 °C; υ_{max}/cm^{-1} (solid) 2977, 2930, 2796, 1641, 1597; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.83 (3H, s, NCHCC**H**$_3$), 1.00 (1H, dt, *J* 12.7, 7.8 Hz) and 1.92 (1H, ddd, *J* 12.7, 6.9, 5.4 Hz, NTsCH$_2$C**H**$_2$), 2.43 (1H, m, CH$_2$=CHC**H**), 2.45 (3H, s, PhC**H**$_3$), 2.63 (1H, t, *J* 9.6 Hz) and 2.80 (1H, dd, *J* 9.9, 7.4 Hz, NBnC**H**$_2$), 3.34 (1H, ddd, 11.4, 7.9, 6.9 Hz) and 3.48 (1H, ddd, *J* 11.4, 7.8, 5.4 Hz, NTsC**H**$_2$), 3.95 (1H, d, *J* 14.1 Hz) and 4.16 (1H, d, *J* 14.1 Hz, NC**H**$_2$Ph), 4.77 (1H, s, NC**H**N), 4.97 (1H, ddd, *J* 17.1, 2.9, 1.8 Hz) and 5.02 (1H, ddd, *J* 10.3, 1.8, 0.9 Hz, CH=C**H**$_2$), 5.64 (1H, ddd, *J* 17.1, 10.3, 8.1 Hz, C**H**=CH$_2$), 7.23-7.26 (1H, m) and 7.27-7.36 (6H, m, Aromatic C**H**), 7.78 (2H, app. d, *J* 8.2 Hz, SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 (Ph**C**H$_3$), 24.8 (NCHC**C**H$_3$), 33.6 (NTsCH$_2$**C**H$_2$), 49.3 (NTs**C**H$_2$), 51.0 (CH$_2$=CH**C**H), 53.4 (NBn**C**H$_2$), 54.7 (N**C**H$_2$Ph), 54.8 (NCH**C**), 90.5 (N**C**HN), 117.1 (CH=**C**H$_2$), 126.6, 127.4, 128.1, 128.5 and 129.6 (Aromatic **C**H), 135.8 (**C**H=CH$_2$), 136.4 (SO$_2$**C**), 139.9 (NCH$_2$**C**), 143.3 (SO$_2$CCHCH**C**); *m*/*z* (CI) 397 (MH$^+$, 100%), 277 (39), 241 (69); HRMS found 397.1956, $C_{23}H_{29}N_2O_2S$ (MH$^+$) requires 397.1950.

(±)-2-((3*S*,3a*R*)-1-Benzyl-3a-methyl-6-tosyl-octahydropyrrolo[2,3-b]pyrrol-3-yl) ethanol (313) and **(±)-(3*S*,3a*R*)-1-benzyl-3-ethyl-3a-methyl-6-tosyl-octahydro pyrrolo[2,3-b]pyrrole (312)**



To a degassed (× 5) solution of alkene **289** (2.00 g, 5.05 mmol) in THF (46 mL) was added Wilkinson's catalyst (137 mg, 0.15 mmol) and the solution immediately degassed (× 5). To this, pinacolborane was added (2.00 mL, 13.8 mmol) and the solution was degassed once more (× 5) and the resulting mixture stirred at rt for 18 h. The reaction mixture was cooled to 0 °C and H_2O (47 mL) and $NaBO_3.4H_2O$ (2.75 g, 17.9 mmol) were added successively; the solution was stirred at 0 °C for 15 min and then at rt for 5 h. H_2O (50 mL) was added and the organic material was extracted into EtOAc (3 × 150 mL), washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude alcohol. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→4:1) gave bicycle **313** (101 mg, 5%) as a thick yellow oil: υ_{max}/cm^{-1} (neat), 2960, 2928, 2874, 1598; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.74-0.82 (6H, m, CH$_2$C**H**$_3$ and NCHCC**H**$_3$), 1.01 (1H, dt, *J* 12.8, 7.2 Hz, NTsCH$_2$C**H**H), 1.11 (1H, m) and 1.27-1.38 (1H, m, C**H**$_2$CH$_3$), 1.63-1.72 (1H, m, C**H**CH$_2$CH$_3$), 1.92 (1H, m, NTsCH$_2$CH**H**), 2.38 (1H, t, *J* 9.8 Hz, NBnC**H**H), 2.42 (3H,

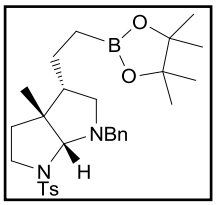
s, PhC**H**$_3$), 2.82 (1H, dd, *J* 9.8, 7.9 Hz, NBnCH**H**), 3.34 (1H, dt, *J* 11.2, 7.0 Hz) and 3.44 (1H, dt, *J* 11.2, 7.2 Hz, NTsC**H**$_2$), 3.95 (1H, d, *J* 14.3 Hz) and 4.14 (1H, d, *J* 14.3 Hz, NC**H**$_2$Ph), 4.74 (1H, s, NC**H**N), 7.20-7.40 (7H, m, Aromatic C**H**), 7.76 (2H, d, *J* 8.0 Hz, SO_2CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.3 (CH_2**C**H_3), 21.7 (Ph**C**H_3), 21.9 (**C**H_2CH_3), 24.9 (NCHC**C**H_3), 32.8 (NTsCH_2**C**H_2), 48.1 (**C**HCH_2CH_3), 49.7 (NTs**C**H_2), 52.6 (NCH**C**CH_3), 55.0 (NBn**C**H_2), 56.0 (NBn**C**H_2), 91.4 (N**C**HN), 126.7, 127.6, 128.2, 128.5 and 129.7 (Aromatic **C**H), 136.4, 140.3 and 143.4 (Aromatic **C**); *m*/*z* (CI) 399 (MH^+, 100%), 243 (14); HRMS found 399.2106, $C_{23}H_{31}N_2O_2S$ (MH^+) requires 399.2106.



Further elution (SiO_2, petrol/EtOAc 7:3→1:1) gave desired alcohol **312** (1.71 g, 82%) as a yellow oil: υ_{max}/cm^{-1} (neat) 3500 br, 2953, 2930, 2873, 1598; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.78 (3H, s, NCHCC**H**$_3$), 1.05 (1H, ddd, *J* 12.9, 7.6, 6.9 Hz, C**H**HCH_2NTs), 1.36 (1H, dddd, *J* 13.3, 10.5, 7.0, 5.6 Hz) and 1.57 (1H, dddd, *J* 13.3, 7.6, 7.0, 4.3 Hz, C**H**$_2CH_2$OH), 1.87 (1H, dddd, *J* 10.5, 9.8, 7.8, 4.3 Hz, C**H**CH_2NBn), 1.92 (1H, dt, *J* 12.9, 6.9 Hz, CH**H**CH_2NTs), 2.42 (3H, s, PhC**H**$_3$), 2.45 (1H, t, *J* 9.8 Hz) and 2.81 (1H, dd, *J* 9.8, 7.8 Hz, C**H**$_2$NBn), 3.35 (1H, dt, *J* 11.1, 6.9 Hz) and 3.43 (1H, ddd, *J* 11.1, 7.6, 6.4 Hz, C**H**$_2$NTs), 3.46 (1H, dt, *J* 10.4, 7.0 Hz) and 3.52 (1H, ddd, *J* 10.4, 7.6, 5.6 Hz, C**H**$_2$OH), 3.95 (1H, d, *J* 14.1 Hz) and 4.11 (1H, d, *J* 14.1 Hz, NC**H**$_2$Ph), 4.72 (1H, s, NC**H**N), 7.22 (1H, m, Aromatic C**H**), 7.26-7.32 (6H, m, Aromatic C**H**), 7.56 (2H, d, *J* 6.6 Hz, SO_2CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 (Ph**C**H_3), 24.4 (NCHC**C**H_3), 31.9 (**C**H_2CH_2OH), 32.8 (**C**H_2CH_2NTs), 42.7 (**C**HCH_2NBn), 49.5 (**C**H_2NTs), 52.7 (NCH**C**), 54.9 (N**C**H_2Ph), 55.9 (**C**H_2NBn), 61.9 (**C**H_2OH), 90.9 (N**C**HN), 126.7 (Aromatic **C**H), 127.6 (SO_2C**C**H), 128.3, 128.5 and 129.8 (Aromatic **C**H), 136.2 (Aromatic **C**), 140.1 (NCH_2**C**), 143.5 (Aromatic **C**); *m*/*z* (CI) 415 (MH^+, 55%), 120 (100); HRMS found 415.2041, $C_{23}H_{31}N_2O_3S$ (MH^+) requires 415.2055.

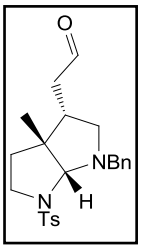
(±)-(*R*)-3-((*S*)-1-Hydroxybut-3-en-2-yl)-3-methylpyrrolidin-2-one (311)

To a degassed (× 5) solution of alkene **289** (50.0 mg, 0.13 mmol) in THF (1.2 mL) was added Wilkinson's catalyst (3.50 mg, 3.78 μmol) and the resulting mixture immediately degassed (× 5). Pinacolborane (54.0 μL, 0.37 mmol) was then added and the solution



stirred for 18 h. After this time, H_2O (1 mL) was added and the organic material extracted into Et_2O (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) gave borane **311** (43.0 mg, 65%) as a yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2976, 2927, 1598; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.56-0.68 (2H, m, C**H**$_2$B), 0.76 (3H, s, NTsCHCC**H**$_3$), 1.03 (1H, dt, *J* 12.8, 7.2 Hz, NTsCH$_2$C**H**H), 1.15-1.18 (13H, m, 2 × C(C**H**$_3$)$_2$ and C**H**HCH$_2$B), 1.40 (1H, m, CH**H**CH$_2$B), 1.66-1.72 (1H, m, NBnCH$_2$C**H**), 1.93 (1H, dt, *J* 12.8, 7.0 Hz, NTsCH$_2$CH**H**), 2.40 (1H, t, *J* 9.8 Hz, NBnC**H**H), 2.42 (3H, s, PhC**H**$_3$), 2.80 (1H, dd, *J* 9.8, 7.7 Hz, NBnCH**H**), 3.35 (1H, dt, *J* 11.0, 6.7 Hz) and 3.40 (1H, dt, *J* 11.0, 7.2 Hz, NTsC**H**$_2$), 3.95 (1H, d, *J* 14.1 Hz) and 4.10 (1H, d, *J* 14.1 Hz, NC**H**$_2$Ph), 4.71 (1H, s, NC**H**N), 7.21 (1H, m, Aromatic C**H**), 7.26-7.33 (6H, m, Aromatic C**H** and SO$_2$CCHC**H**), 7.73 (2H, d, *J* 8.3 Hz, SO$_2$CC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.1 (Ph**C**H$_3$), 23.0 (**C**H$_2$CH$_2$B), 24.7 (NTsCHC**C**H$_3$), 24.9 (2 × C(**C**H$_3$)$_2$), 32.7 (NTsCH$_2$**C**H$_2$), 47.4 (NBnCH$_2$**C**H), 48.5 (NTs**C**H$_2$), 52.7 (NTsCH**C**CH$_3$), 55.0 (N**C**H$_2$Ph), 56.5 (NBn**C**H$_2$), 83.2 (2 × **C**(CH$_3$)$_2$), 91.4 (N**C**HN), 126.6, 127.3, 128.3, 128.6 and 129.9 (Aromatic **C**H), 136.3 (SO$_2$**C**), 140.2 (NCH$_2$**C**), 143.4 (SO$_2$CCHCH**C**); *m*/*z* (CI) 525 (100), 369 (8); HRMS found 525.2962, $C_{29}H_{42}N_2O_4SB$ (MH^+) requires 525.2958.

(±)-2-((3*S*,3a*R*)-1-Benzyl-3a-methyl-6-tosyl-octahydropyrrolo[2,3-b]pyrrol-3-yl)acetaldehyde (290)

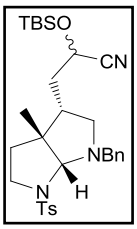


To a solution of alcohol **312** (322 mg, 0.78 mmol) in DCM (10.5 mL) at 0 °C was added pyridine (0.54 mL, 6.70 mmol) followed by DMP (708 mg, 1.67 mmol) and the solution stirred at rt for 18 h. Sat. $Na_2S_2O_3$ (10 mL) and sat. $NaHCO_3$ (10 mL) were then added and the solution stirred vigorously for 1 h. The organic material was extracted with DCM (3 × 30 mL), washed with sat. $CuSO_4$ (20 mL), H_2O (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3→3:2) afforded aldehyde **290** (190 mg, 59%) as a thick yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2956, 2922, 1723, 1598; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.78 (3H, s, NCHCC**H**$_3$), 1.11 (1H, ddd, *J* 12.8, 7.5, 6.4 Hz) and 1.88 (1H, dt, *J* 12.8, 7.0 Hz, C**H**$_2$CH$_2$NTs), 2.28-2.36 (2H, m,

C**H**HCHO and C**H**CH_2NBn), 2.39-2.49 (2H, m, CH**H**CHO and C**H**HNBn), 2.43 (3H, s, PhC**H**$_3$), 2.89 (1H, dd, *J* 10.2, 7.4 Hz, CH**H**NBn), 3.39 (1H, ddd, *J* 10.9, 7.2, 6.4 Hz) and 3.44 (1H, ddd, *J* 10.9, 7.5, 6.8 Hz, C**H**$_2$NTs), 4.02 (2H, s, NC**H**$_2$Ph), 4.68 (1H, s, NC**H**N), 7.20-7.25 (1H, m) and 7.27-7.33 (4H, m, Aromatic C**H**), 7.28 (2H, d, *J* 8.3 Hz, 2 × SO_2CCHC**H**), 7.76 (2H, d, *J* 8.3 Hz, 2 × SO_2CC**H**), 9.66 (1H, m, C**H**O); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.7 (Ph**C**H_3), 24.1 (NCHC**C**H_3), 33.1 (**C**H_2CH_2NTs), 39.8 (**C**HCH_2NBn), 43.8 (**C**H_2CHO), 49.2 (**C**H_2NTs), 52.3 (NCH**C**), 55.0 (N**C**H_2Ph), 55.7 (**C**H_2NBn), 90.4 (N**C**HN), 126.8 (Aromatic **C**H), 127.6 (SO_2C**C**H), 128.3, 128.6 and 129.8 (Aromatic **C**H), 136.1, 139.7 and 143.6 (Aromatic **C**), 200.9 (**C**HO); *m*/*z* (CI) 413 (MH^+, 100%); HRMS found 413.1902, $C_{23}H_{29}N_2O_3S$ (MH^+) requires 413.1899.

(±)-3-((3*S*,3a*R*)-1-Benzyl-3a-methyl-6-tosyl-octahydropyrrolo[2,3-b]pyrrol-3-yl)-2-(tert-butyldimethylsilyloxy)propanenitrile (314)

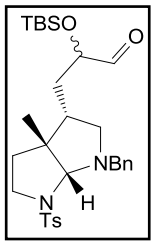
[Diastereoisomer one (D-1) : Diastereoisomer two (D-2) = 1:1]



To a solution of aldehyde **290** (75.0 mg, 0.18 mmol) in DCM (1.1 mL) was added TBSCN (52.0 mg, 0.37 mmol) followed by 0.3 M LiCl in DCM (sonicated for 30 min, 8.00 µL, 2.40 µmol) and the mixture stirred for 3 d. The reaction was quenched with H_2O (1 mL) and organic material extracted into EtOAc (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to give the crude material. Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→17:3) gave a mixture of diastereomeric nitriles **314** (70.0 mg, 70%) as a thick colourless oil: υ_{max}/cm^{-1} (DCM cast) 2956, 2930, 2860, 1599; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (3H, s), 0.03 (3H, s) 0.12 (3H, s) and 0.14 (3H, s, Si(C**H**$_3$)$_2^{D-1}$ and Si(C**H**$_3$)$_2^{D-2}$), 0.78 (3H, s) and 0.80 (3H, s, C(C**H**$_3$)$_3^{D-1}$ and C(C**H**$_3$)$_3^{D-2}$), 0.83 (6H, s) and 0.83 (18H, s, C(C**H**$_3$)$_3^{D-1}$, C(C**H**$_3$)$_3^{D-2}$, NTsCHCC**H**$_3^{D-1}$ and NTsCHCC**H**$_3^{D-2}$), 1.09-1.19 (2H, m, NTsCH_2C**H**H^{D-1} and NTsCH_2C**H**H^{D-2}), 1.56-1.76 (2H, m) and 1.88-2.00 (3H, m, C**H**$_2$CHCN^{D-1}, C**H**$_2$CHCN^{D-2}, NBnCH_2C**H**$^{D-1}$), 2.02-2.12 (1H, m, NBnCH_2C**H**$^{D-2}$), 2.46 (6H, s, PhC**H**$_3^{D-1}$ and PhC**H**$_3^{D-2}$), 2.50 (1H, t, *J* 9.8 Hz), 2.55 (1H, t, *J* 9.8 Hz) and 2.88 (2H, dt, *J* 9.8, 7.8 Hz, NBnC**H**$_2^{D-1}$ and NBnC**H**$_2^{D-2}$), 3.38-3.50 (4H, m, NTsC**H**$_2^{D-1}$and NTsC**H**$_2^{D-2}$), 4.03 (1H, d, *J* 14.0 Hz), 4.03 (1H, d, *J* 14.2 Hz), 4.08 (1H, d, *J* 14.0 Hz) and 4.10 (1H, d, *J* 14.2 Hz, NC**H**$_2$Ph^{D-1} and NC**H**$_2$Ph^{D-2}), 4.25 (1H, t, *J* 6.8 Hz) and 4.30 (1H, dd, *J* 7.6, 4.0 Hz, C**H**CN^{D-1} and C**H**CN^{D-2}), 4.72 (1H, s) and

4.73 (1H, s, NC**H**N^{D-1} and NC**H**N^{D-2}), 7.20-7.28 (2H, m) 7.26-7.40 (12H, m, 5 × Aromatic C**H**$^{D-1}$, 5 × Aromatic C**H**$^{D-2}$, $SO_2CCHC\mathbf{H}^{D-1}$ and $SO_2CCHC\mathbf{H}^{D-2}$), 7.78 (2H, d, *J* 8.3 Hz) and 7.79 (2H, d, *J* 8.2 Hz, $SO_2CC\mathbf{H}^{D-1}$ and $SO_2CC\mathbf{H}^{D-2}$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –5.5, –5.3, –5.2 and –5.1 ($Si(\mathbf{C}H_3)_2^{D-1}$ and $Si(\mathbf{C}H_3)_2^{D-2}$), 18.0 and 18.0 ($\mathbf{C}(CH_3)_3^{D-1}$ and $\mathbf{C}(CH_3)_3^{D-2}$), 21.7 ($Ph\mathbf{C}H_3^{D-1}$ and $Ph\mathbf{C}H_3^{D-2}$), 23.6, 23.7, 25.5 and 25.6 ($C(\mathbf{C}H_3)_3^{D-1}$, $C(\mathbf{C}H_3)_3$, $NTsCHC\mathbf{C}H_3^{D-1}$ and $NTsCHC\mathbf{C}H_3^{D-2}$), 32.6 and 32.7 ($NTsCH_2\mathbf{C}H_2^{D-1}$ and $NTsCH_2\mathbf{C}H_2^{D-2}$), 35.7 and 36.1 ($\mathbf{C}H_2CHCN^{D-1}$ and $\mathbf{C}H_2CHCN^{D-2}$), 41.7 and 42.6 ($NBnCH_2\mathbf{C}H^{D-1}$ and $NBnCH_2\mathbf{C}H^{D-2}$), 49.1 and 49.2 ($NTs\mathbf{C}H_2^{D-1}$ and $NTs\mathbf{C}H_2^{D-2}$), 52.7 and 53.0 ($NTsCH\mathbf{C}CH_3^{D-1}$ and $NTsCH\mathbf{C}CH_3^{D-2}$), 54.9 and 54.9 ($N\mathbf{C}H_2Ph^{D-1}$ and $N\mathbf{C}H_2Ph^{D-2}$), 55.4 and 55.7 ($NBn\mathbf{C}H_2^{D-1}$ and $NBn\mathbf{C}H_2^{D-2}$), 60.8 and 61.8 ($\mathbf{C}HCN^{D-1}$ and $\mathbf{C}HCN^{D-2}$), 90.0 and 90.2 ($N\mathbf{C}HN^{D-1}$ and $N\mathbf{C}HN^{D-2}$), 119.7 and 119.8 ($\mathbf{C}N^{D-1}$ and $\mathbf{C}N^{D-2}$), 126.8, 126.8, 127.6, 128.3, 128.4, 128.5, 128.5 and 129.8 (Aromatic $\mathbf{C}H^{D-1}$ and Aromatic $\mathbf{C}H^{D-2}$), 136.0 and 136.1 ($SO_2\mathbf{C}^{D-1}$ and $SO_2\mathbf{C}^{D-2}$), 139.8 and 139.8 ($NCH_2\mathbf{C}^{D-1}$ and $NCH_2\mathbf{C}^{D-2}$), 143.6 ($SO_2CCHCH\mathbf{C}^{D-1}$ and $SO_2CCHCH\mathbf{C}^{D-2}$); *m*/*z* (CI) 554 ($MH^+$, 100%), 398 (12), 107 (37); HRMS found 554.2867, $C_{30}H_{44}N_3O_3SSi$ (MH^+) requires 554.2873.

(±)-3-((3*S*,3a*R*)-1-Benzyl-3a-methyl-6-tosyl-octahydropyrrolo[2,3-b]pyrrol-3-yl)-2-(*tert*-butyldimethylsilyloxy)propanal (282)



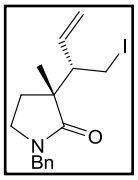
[Major diastereoisomer (MAJ) : Minor diastereoisomer MIN = 1.6:1]
To a solution of nitrile **314** (50.0 mg, 0.09 mmol) in toluene (176 µL) at –78 ºC was added DIBAL (1 M in toluene, 177 µL, 0.18 mmol) dropwise and the solution stirred for 2 h. After this time, MeOH (88 µL) was added and the solution was warmed to 0 ºC and stirred for 1.5 h. H_2SO_4 (0.5 M, 88 µL) was then added, the mixture stirred vigorously for 1 h and H_2O (0.5 mL) added. The organic material was extracted into EtOAc (3 × 2mL), washed with brine (2 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 1:9→3:17) gave aldehyde **282** (15.0 mg, 30%) as a pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 2954, 2928, 2856, 1736, 1598; ^{1}H NMR ($CDCl_3$, 600 MHz) δ –0.09 (3H, s, $Si(C\mathbf{H}_3)_2^{MIN}$), –0.08 (3H, s, $Si(C\mathbf{H}_3)_2^{MAJ}$), –0.02 (3H, s, $Si(C\mathbf{H}_3)_2^{MIN}$), –0.02 (3H, s, $Si(C\mathbf{H}_3)_2^{MAJ}$), 0.74 (3H, s, $NCHCC\mathbf{H}_3^{MAJ}$), 0.75 (3H, s, $NCHCC\mathbf{H}_3^{MIN}$), 0.80 (9H, s, $C(C\mathbf{H}_3)_3^{MIN}$), 0.84 (9H, s, $C(C\mathbf{H}_3)_3^{MAJ}$), 1.39-1.46 (2H, m) and 1.52-1.66

(2H, m, C**H**$_2$CHOTBS^{MAJ} and C**H**$_2$CHOTBS^{MIN}), 1.84-1.97 (4H, m, NBnCH$_2$C**H**^{MAJ}, NBnCH$_2$C**H**^{MIN}, NTsCH$_2$C**H**$_2^{MAJ}$ and NTsCH$_2$C**H**$_2^{MIN}$), 2.43 (6H, s, PhC**H**$_3^{MAJ}$ and PhC**H**$_3^{MIN}$), 2.45 (1H, t, *J* 9.8 Hz, NBnC**H**H^{MAJ}), 2.46 (1H, t, *J* 9.8 Hz, NBnC**H**H^{MIN}), 2.77-2.84 (2H, m, NBnCH**H**^{MAJ} and NBnCH**H**^{MIN}), 3.33-3.44 (4H, m, NTsC**H**$_2^{MAJ}$ and NTsC**H**$_2^{MIN}$), 3.77 (1H, ddd, *J* 8.9, 3.2, 1.4 Hz, C**H**OTBS^{MAJ}), 3.83 (1H, td, *J* 6.6, 1.9 Hz, C**H**OTBS^{MIN}), 3.97 (1H, d, *J* 14.1 Hz, NC**H**HPh^{MIN}), 3.98 (1H, d, *J* 14.1 Hz, NC**H**HPh^{MAJ}), 4.08 (2H, d, *J* 14.1 Hz, NCH**H**Ph^{MAJ} and NCH**H**Ph^{MIN}), 4.69 (1H, s, NC**H**N^{MIN}), 4.71 (1H, s, NC**H**N), 7.18-7.36 (Aromatic C**H** and Aromatic C**H**^{MIN}), 7.72-7.79 (4H, m, NCC**H**CHCMe^{MAJ} and NCC**H**CHCMe^{MIN}), 9.47 (1H, d, *J* 1.9 Hz, C**H**O^{MIN}), 9.52 (1H, d, *J* 1.4 Hz, C**H**O^{MAJ}); ^{13}C NMR ($CDCl_3$, 150 MHz) δ; *m*/*z* (CI) 557 (MH^+, 100%), 401 (15); HRMS found 557.2854, $C_{30}H_{45}N_2O_4SSi$ (MH^+) requires 557.2869.

A NEW METHOD FOR ALCOHOL ACTIVATION

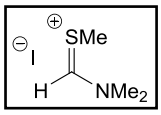
Alcohol Iodination

(±)-*N*-Benzyl-3-(1-iodobut-3-en-2-yl)-3-methylpyrrolidin-2-one (317)



To a solution of alcohol **99** (98.0 mg, 0.36 mmol) in THF (5 mL) was added MeI (62.3 μL, 0.72 mmol) and the solution stirred at reflux for 2 days. The organic material was extracted with DCM (3 × 5 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give iodide **317** (133 mg, 82%) as a white solid: mpt. 108-111 °C; υ_{max}/cm^{-1} (solid) 2885, 1681; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.21 (3H, s, C**H**$_3$), 1.61 (1H, ddd, *J* 13.1, 8.0, 3.9 Hz) and 2.06 (1H, ddd, *J* 13.1, 8.9, 7.4 Hz, NCH$_2$C**H**$_2$), 2.66 (1H, td, *J* 10.0, 2.9 Hz, C**H**CH$_2$I), 3.08-3.20 (3H, m, C**H**HI and NC**H**$_2$CH$_2$), 3.43 (1H, dd, *J* 9.5, 2.9 Hz, CH**H**I), 4.44 (2H, s, NC**H**$_2$Ph), 5.17 (1H, dd, *J* 16.9, 1.6 Hz) and 5.28 (1H, dd, *J* 10.0, 1.6 Hz, CH=C**H**$_2$), 5.42 (1H, dt, *J* 16.9, 10.0 Hz, C**H**=CH$_2$), 7.21-7.35 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 7.4 (**C**H$_2$I), 23.7 (**C**H$_3$), 27.9 (NCH$_2$**C**H$_2$), 43.4 (N**C**H$_2$CH$_2$), 46.8 (N**C**H$_2$Ph), 47.7 (**C**Me), 53.5 (**C**HCH$_2$I), 120.4 (CH**C**H$_2$), 127.7, 128.2 and 128.7 (Aromatic **C**H), 136.0 (**C**HCH$_2$), 136.3 (Aromatic **C**), 177.1 (**C**=O).

***N*,*N*,*N*-Trimethylmethanethioamide iodide (327)**



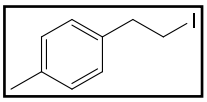
To a solution of HCSNMe$_2$ (**318**, 2.90 mL, 33.7 mmol) in dry ether (70 mL) was added MeI (2.30 mL, 37.0 mmol) and the solution stirred at rt for 18 h. The precipitate was collected by filtration under argon and was washed with cold dry ether (2 × 25 mL) and dried *in vacuo* for 10 min to give salt **327** (7.47 g, 96%) as a crystalline white solid which was stored in a freezer under argon: mpt. 131-132 °C; υ_{max}/cm^{-1} (solid) 2983, 1639, 1619, 1442, 1408; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.16 (3H, s, SC**H**$_3$), 3.40 (3H, s) and 3.90 (3H, s, N(C**H**$_3$)$_2$), 11.14 (1H, s, **H**C=SMe); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.6 (S**C**H$_3$), 42.7 and 48.9 (N(**C**H$_3$)$_2$), 183.5 (H**C**=SMe); *m*/*z* (CI) 104 ([M–I]$^+$, 5%), 92 (10), 91 (11), 90 (100); HRMS found 104.0537, $C_4H_{10}NS$ ([M–I]$^+$) requires 104.0534.

General procedure for iodinations – *Method A*

To a solution of alcohol (1.0 equiv.) in toluene/THF (0.20-0.25M substrate or 0.14 M substrate for allylic alcohols) at 85 °C (or 55 ºC for allylic alcohols) in toluene or reflux in THF was added salt **327** (1.5 equiv.) and imidazole (0.5 equiv. or 1 equiv. for secondary alcohols) successively. Upon completion (reaction monitored by TLC or ^{1}H NMR), the solvent was removed *in vacuo* to give the crude product. Purification by flash chromatography (as described) afforded pure iodides.

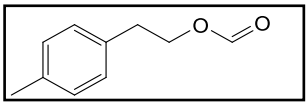
For yields and reaction times, please refer to Table 7, section 4.1.3.3.

1-(2-Iodoethyl)-4-methylbenzene (324)



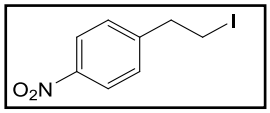
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol) afforded iodide **324** as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3019, 2920, 1513; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (3H, s, C**H**$_3$), 3.16 (2H, t, *J* 8.0 Hz, PhC**H**$_2$), 3.36 (2H, t, *J* 8.0 Hz, C**H**$_2$I), 7. 11 (2H, d, *J* 8.0 Hz) and 7.16 (2H, d, *J* 8.0 Hz, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.0 (**C**H$_2$I), 21.2 (**C**H$_3$), 40.1 (Ph**C**H$_2$), 128.3 and 129.4 (Aromatic **C**H), 136.6 (Me**C**), 137.7 (**C**CH$_2$CH$_2$I); *m*/*z* (EI) 246 (M^+, 23%), 167 (9), 149 (28), 128 (47), 127 (33), 120 (69), 119 (100); HRMS found 245.9897, $C_9H_{11}I$ (M^+) requires 245.9900.

4-Methylphenethyl formate (325)



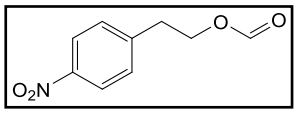
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1) afforded formate **325** as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 2924, 1719, 1516; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (3H, s, C**H**$_3$), 2.98 (2H, t, *J* 7.1 Hz, C**H**$_2$O), 4.41 (2H, td, *J* 7.1, 0.8 Hz, C**H**$_2$CH$_2$O), 7.16 (4H, s, Aromatic C**H**), 8.07 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1 (**C**H$_3$), 34.6 (**C**H$_2$O), 64.6 (**C**H$_2$CH$_2$O), 128.8 and 129.4 (Aromatic **C**H), 134.4 (CH$_3$**C**), 136.4 (CH$_2$**C**), 161.1 (**C**HO); *m*/*z* (EI) 118 ([M–CO_2H_2]$^+$, 100%); HRMS found 118.0786, C_9H_{10} ([M–CO_2H_2]$^+$) requires 118.0783.

1-(2-Iodoethyl)-4-nitrobenzene



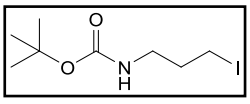
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 97:3) afforded the iodide as a white solid: mpt. 98-101 °C [Lit.[127] 97-98 °C]; υ_{max}/cm^{-1} (solid) 3053, 1601, 1520, 1346; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.31 (2H, t, *J* 7.3 Hz, PhC**H**$_2$), 3.41 (2H, t, *J* 7.3 Hz, C**H**$_2$I), 7.37-7.40 (2H, m, NO_2CC**H**), 8.19-8.23 (2H, m, CH_2CC**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7 (**C**H_2I), 39.5 (Ph**C**H_2), 124.0 (CH_2C**C**H), 129.4 (NO_2C**C**H), 147.1 (NO_2**C**), 147.7 (CH_2**C**); *m*/*z* (EI) 277 (M^+, 59%), 261 (14), 242 (8), 231 (4), 150 (100); HRMS found 276.9592, $C_8H_8O_2NI^+$ (M^+) requires 276.9594.

4-Nitrophenethyl formate



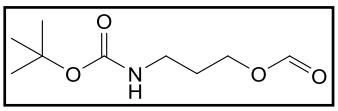
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1) afforded the formate as a white solid: mpt. 65-67 °C; υ_{max}/cm^{-1} (solid) 3081, 2968, 1713, 1697, 1606, 1597, 1515, 1342; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.11 (2H, t, *J* 6.7 Hz, C**H**$_2$$CH_2O$), 4.45 (2H, td, *J* 6.7, 0.7 Hz, C**H**$_2$O), 7.41 (2H, m, CH_2CC**H**), 8.04 (1H, s, C**H**O), 8.20 (2H, m, NO_2CC**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.8 (**C**H_2CH_2O), 63.4 (**C**H_2O), 123.9 (NO_2C**C**H), 129.8 (CH_2C**C**H), 145.2 (NO_2**C**), 147.1 (CH_2**C**), 160.7 (**C**HO); *m*/*z* (CI) 196 (MH^+, 10%), 150 (100); HRMS found 196.0606, $C_9H_{10}NO_4$ (MH^+) requires 196.0610.

***Tert*-butyl 3-iodopropylcarbamate**



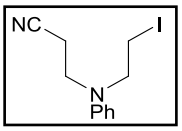
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 19:1) afforded the iodide as a yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3341 br, 2976, 2931, 1683, 1512; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (9H, s, C(C**H**$_3$)$_3$), 1.99 (2H, quin, *J* 6.7 Hz, $NHCH_2C$**H**$_2$), 3.18 (2H, t, *J* 6.7 Hz, NHC**H**$_2$), 3.16-3.21 (2H, m, C**H**$_2$I), 4.74 (1H, br s, N**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.2 (**C**H_2I), 28.5 (C(**C**H_3)$_3$), 33.5 ($NHCH_2$**C**H_2), 41.1 (NH**C**H_2), 79.4 (**C**Me_3), 156.0 (**C**=O); *m*/*z* (FAB^+) 308 (MNa^+, 49%), 286 (50), 230 (100); HRMS found 308.0118, $C_8H_{16}O_2NINa$ (MNa^+) requires 308.0123.

3-(*Tert*-butoxycarbonyl)propyl formate



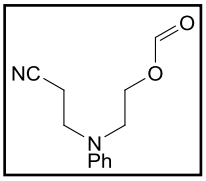
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→85:15) afforded the formate as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3355 br, 2977, 2931, 1712, 1689; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (9H, s, C(C**H**$_3$)$_3$), 1.87 (2H, quin, *J* 6.5 Hz, NHCH$_2$C**H**$_2$), 3.23 (2H, m, NHC**H**$_2$), 4.26 (2H, t, *J* 6.5 Hz, C**H**$_2$O), 4.69 (1H, br s, N**H**), 8.08 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.6 (C(**C**H$_3$)$_3$), 31.2 (HCH$_2$**C**H$_2$), 39.4 (NH**C**H$_2$), 63.6 (**C**H$_2$O), 80.0 (**C**Me$_3$), 163.2 (**C**HO), 194.0 (**C**=ONH); *m*/*z* (CI) 204 (MH^+, 46%), 158 (100); HRMS found 204.1231, $C_9H_{18}NO_4$ (MH^+) requires 204.1236.

3-((2-Iodoethyl)(phenyl)amino)propanenitrile



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded the iodide as a pale yellow solid: mpt. 59-62 °C; υ_{max}/cm^{-1} (solid) 3025, 2955, 2247, 1596, 1502; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (2H, t, *J* 6.8 Hz, C**H**$_2$CN), 3.27 (2H, t, *J* 8.1 Hz, C**H**$_2$I), 3.76 (2H, t, *J* 6.88 Hz, C**H**$_2$CH$_2$CN), 3.80 (2H, t, *J* 8.1 Hz, C**H**$_2$CH$_2$I), 6.70 (2H, d, *J* 8.5 Hz, NCC**H**), 6.83-6.86 (1H, m, NCCHCHC**H**), 7.27-7.33 (2H, m, NCCHC**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.7 (**C**H$_2$I), 16.4 (**C**H$_2$CN), 47.5 (**C**H$_2$CH$_2$CN), 54.6 (**C**H$_2$CH$_2$I), 112.7 (NC**C**H), 118.2 (Aromatic **C**), 118.6 (NCCHCH**C**H), 130.0 (NCCH**C**H), 145.2 (**C**N); *m*/*z* (EI) 300 (M^+, 62%), 260 (86), 232 (8), 173 (23), 160 (10), 159 (100); HRMS found 300.0122, $C_{11}H_{13}N_2I$ (M^+) requires 300.0118.

2-((2-Cyanoethyl)(phenyl)amino)ethyl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→85:15) afforded the formate as a pale yellow oil: υ_{max}/cm^{-1} (neat) 3061, 2935, 2248, 1717, 1598, 1504; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (2H, t, *J* 7.0 Hz, CNC**H**$_2$), 3.72 (2H, t, *J* 6.0 Hz, C**H**$_2$CH$_2$O), 3.76 (2H, t, *J* 7.0 Hz, CNCH$_2$C**H**$_2$), 4.35 (2H, td, *J* 6.0, 0.6 Hz, C**H**$_2$O), 6.73 (2H, m, NCC**H**), 6.83 (1H, m, NCCHCHC**H**), 7.30 (2H, m, NCCHC**H**);

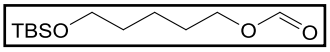
^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0 (CN**C**H_2), 47.8 (CNCH_2**C**H_2), 50.1 (**C**H_2CH_2O), 61.2 (**C**H_2O), 112.9 (NC**C**H), 118.2 (Aromatic **C**), 118.5 (NCCHCH**C**H), 129.9 (NCCH**C**H), 145.8 (**C**N), 160.8 (**C**HO); *m*/*z* (FAB$^+$) 219 (MH^+, 88%), 218 (100); HRMS found 219.1129, $C_{12}H_{15}O_2N_2$ (MH^+) requires 219.1134.

***Tert*-butyl(5-iodopentyloxy)dimethylsilane**

The crude material was obtained using *Method A.* Purification by 

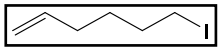
flash chromatography (SiO_2, hexane) afforded the iodide as a colourless oil: υ_{max}/cm^{-1} (neat) 2928, 2856; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (6H, s, Si(C**H**$_3$)$_2$), 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.41-1.50 (2H, m, OCH_2CH_2C**H**$_2$), 1.50-1.59 (2H, m, C**H**$_2$CH_2I), 1.86 (2H, tt, *J* 7.3, 7.0 Hz, OCH_2C**H**$_2$), 3.21 (2H, t, *J* 7.0 Hz, OC**H**$_2$), 3.62 (2H, t, *J* 6.2 Hz, C**H**$_2$I); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.3 (Si(**C**H_3)$_2$), 7.1 (**C**H_2I), 18.4 (**C**Me$_3$), 26.0 (C(**C**H_3)$_3$), 27.0 (OCH_2CH_2**C**H_2), 31.8 (**C**H_2CH_2I), 33.4 (OCH_2**C**H_2), 62.9 (O**C**H_2); *m*/*z* (CI) 329 (MH^+, 5%), 327 (6), 313 (8), 271 (27), 201 (49), 197 (60), 177 (30), 146 (100); HRMS found 329.0793, $C_{11}H_{26}OSiI$ (MH^+) requires 329.0798.

5-(*Tert*-butyldimethylsilyloxy)pentyl formate

The crude material was obtained using *Method A.* 

Purification by flash chromatography (SiO_2, hexane) afforded the formate as a viscous colourless oil: υ_{max}/cm^{-1} (DCM cast) 2929, 2857, 1729, 1472; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (6H, s, Si(C**H**$_3$)$_2$), 0.90 (9H, s, C(C**H**$_3$)$_3$), 1.41-1.47 (2H, m, TBSOCH_2CH_2C**H**$_2$), 1.53-1.58 (2H, m, TBSOCH_2C**H**$_2$), 1.60-1.67 (2H, m, C**H**$_2$CH_2OCHO), 3.63 (2H, t, *J* 6.3 Hz, TBSOC**H**$_2$), 4.18 (2H, t, *J* 6.8 Hz, C**H**$_2$OCHO), 8.07 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.2 (Si(**C**H_3)$_2$), 18.4 (TBSOCH_2CH_2**C**H_2), 22.3 (C(**C**H_3)$_3$), 26.0 (**C**H_2CH_2OCHO), 28.3 (TBSOCH_2**C**H_2), 32.4 (**C**H_2OCHO), 62.9 (**C**H_2OCHO), 64.1 (**C**Me$_3$), 161.2 (**C**HO); *m*/*z* (CI) 247 (MH^+, 3%), 201 (6), 97 (6), 84 (100); HRMS found 247.1733, $C_{12}H_{27}O_3Si$ (MH^+) requires 247.1729.

6-Iodohex-1-ene

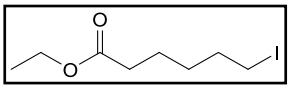


The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, hexane) afforded the iodide as a colourless liquid: υ_{max}/cm^{-1} (DCM cast) 3076, 2930, 2855, 1641; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.55 (2H, m, C**H**$_2$CH$_2$CH$_2$I), 1.78-1.88 (2H, m, C**H**$_2$CH$_2$I), 2.06-2.12 (2H, m, CH$_2$=CHC**H**$_2$), 3.21 (2H, t, *J* 7.1 Hz, C**H**$_2$I), 4.96-5.06 (2H, m, C**H**$_2$=CH), 5.80 (1H, ddt, *J* 17.1, 10.3, 6.7 Hz, CH$_2$=C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.9 (**C**H$_2$I), 29.8 (**C**H$_2$CH$_2$CH$_2$I), 32.7 (CH$_2$=CH**C**H$_2$), 32.9 (**C**H$_2$CH$_2$I), 115.1 (**C**H$_2$=CH), 138.2 (CH$_2$=**C**H); *m*/*z* (EI) 210 (M^+, 13%), 179 (12), 178 (100); HRMS found 209.9894, $C_6H_{11}I$ (M^+) requires 209.9900.

Hex-5-enyl formate

The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, hexane/EtOAc 19:1) afforded the formate as a pale yellow oil: υ_{max}/cm^{-1} (Et_2O cast) 2927, 2856, 1726; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.54 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.65-1.74 (2H, m, C**H**$_2$CH$_2$O), 2.05-2.15 (2H, m, CH$_2$=CHC**H**$_2$), 4.19 (2H, td, *J* 6.7, 0.7 Hz, C**H**$_2$O), 4.96-5.07 (2H, m, C**H**$_2$=CH), 5.80 (1H, ddt, *J* 17.0, 10.3, 6.7 Hz, CH$_2$=C**H**), 8.07 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3 (**C**H$_2$CH$_2$CH$_2$O), 27.9 (**C**H$_2$CH$_2$O), 33.2 (CH$_2$=CH**C**H$_2$), 63.9 (**C**H$_2$O), 114.9 (CH$_2$=**C**H), 138.2 (**C**H$_2$=CH), 161.1 (**C**HO); *m*/*z* (CI) 129 (MH^+, 100%); HRMS found 129.0912, $C_7H_{13}O_2$ (MH^+) requires 129.0916.

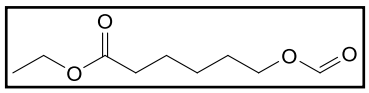
Ethyl 6-iodohexanoate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 49:1) afforded the iodide as a colourless oil: υ_{max}/cm^{-1} (neat) 2935, 2864, 1730; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (3H, t, *J* 7.1 Hz, C**H**$_3$), 1.41-1.48 (2H, m, C**H**$_2$CH$_2$CH$_2$I), 1.62-1.69 (2H, m, C=OCH$_2$C**H**$_2$), 1.85 (2H, quin, *J* 7.3 Hz, C**H**$_2$CH$_2$I), 2.32 (2H, t, *J* 7.6 Hz, C=OC**H**$_2$), 3.20 (2H, t, *J* 7.0 Hz, C**H**$_2$I), 4.14 (2H, q, *J* 7.1 Hz, CH$_3$C**H**$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.6 (**C**H$_2$I), 14.3 (**C**H$_3$), 23.9 (C=OCH$_2$**C**H$_2$), 30.0 (**C**H$_2$CH$_2$CH$_2$I),

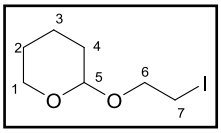
33.2 (**C**H_2CH_2I), 34.1 (C=O**C**H_2), 60.4 (CH_3**C**H_2), 173.5 (**C**=O); *m*/*z* (CI) 271 (MH^+, 37%), 243 (22), 225 (18), 143 (73), 131 (100); HRMS found 271.0197, $C_8H_{16}O_2I$ (MH^+) requires 271.0195.

Ethyl 6-(formyloxy)hexanoate



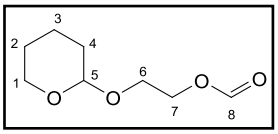
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 97:3) afforded the formate as a yellow oil: υ_{max}/cm^{-1} (DCM cast) 2937, 2869, 1722; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (3H, t, *J* 7.2 Hz, C**H**$_3$), 1.38-1.46 (2H, m, C=OCH_2CH_2C**H**$_2$), 1.61-1.72 (4H, m, C=OCH_2C**H**$_2$ and C**H**$_2$CH_2OCHO), 2.32 (2H, t, *J* 7.4 Hz, C=OC**H**$_2$), 4.14 (2H, q, *J* 7.2 Hz, CH_3C**H**$_2$), 4.18 (2H, t, *J* 6.7 Hz, C**H**$_2$OCHO), 8.07 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.3 (**C**H_3), 24.6 (C=OCH_2**C**H_2), 25.5 (C=OCH_2CH_2**C**H_2), 28.3 (**C**H_2CH_2OCHO), 34.2 (C=O**C**H_2), 60.4 (CH_3**C**H_2), 63.8 (**C**H_2OCHO), 161.2 (**C**HO), 173.6 (O**C**=OCH_2); *m*/*z* (CI) 189 (MH^+, 49%), 144 (23), 143 (100); HRMS found 189.1129, $C_9H_{17}O_4$ (MH^+) requires 189.1127.

2-(2-Iodoethoxy)-tetrahydro-2H-pyran



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol) afforded the iodide as a yellow oil: υ_{max}/cm^{-1} (neat) 2940, 2870; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51-1.67 (4H, m, C^{2}H**H**, C^4**H**H and C^3**H**$_2$), 1.73 (1H, m, C^{4}H**H**), 1.84 (1H, m, C^2**H**H), 3.30 (2H, m, C^7**H**$_2$I), 3.47-3.57 (1H, m, C^1**H**H), 3.73 (1H, dt, *J* 11.1, 6.8 Hz, C^{6}H**H**), 3.86-3.96 (1H, m, C^{1}H**H**), 3.95 (1H, ddd, *J* 11.1, 7.2, 6.5 Hz, C^6**H**H) 4.68 (1H, t, *J* 3.4 Hz, C^5**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6 (**C**^{7}), 19.3 (**C**^{2}), 25.3 (**C**^{3}), 30.5 (**C**^{4}), 62.3 (**C**^{1}), 68.3 (**C**^{6}), 98.8 (**C**^{5}); *m*/*z* (EI) 256 (M^+, 43%), 155 (100); HRMS found 255.9966, $C_7H_{13}O_2I$ (M^+) requires 255.9955.

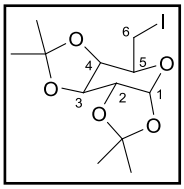
2-(Tetrahydro-2H-pyran-2-yloxy)ethyl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded

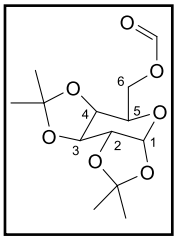
the formate as a yellow oil: υ_{max}/cm^{-1} (neat) 2943, 2873, 1720; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.66 (4H, m, $C^4H\mathbf{H}$, $C^2\mathbf{H}_2$ and $C^3\mathbf{H}H$), 1.67-1.76 (1H, m , $C^4\mathbf{H}H$), 1.70-1.80 (1H, m, $C^3H\mathbf{H}$), 3.52 (1H, m, $C^1\mathbf{H}H$), 3.68 (1H, m, $C^6\mathbf{H}H$), 3.87 (1H, m, $C^1H\mathbf{H}$), 3.96 (1H, m, $C^6H\mathbf{H}$), 4.30-4.42 (2H, m, $C^7\mathbf{H}_2$), 4.65 (1H, m, $C^5\mathbf{H}$), 8.11 (1H, s, $C^8\mathbf{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 ($\mathbf{C}^3$), 25.4 ($\mathbf{C}^4$), 30.5 ($\mathbf{C}^2$), 62.3 ($\mathbf{C}^1$), 63.2 ($\mathbf{C}^7$), 64.9 ($\mathbf{C}^6$), 98.9 ($\mathbf{C}^5$), 161.1 ($\mathbf{C}^8$); *m*/*z* (CI) 175 (MH^+, 100%); HRMS found 175.0976, (MH^+) requires 175.0970.

[(1*S*,2*R*,6*R*,8*S*,9*R*)-8-(Iodomethyl)-4,4,11,11-tetramethyl-3,5,7,10,12-pentaoxatricyclo [7.3.0.0^{2,6}]]dodecane



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 49:1) afforded the iodide as a viscous yellow oil: $[\alpha]_D^{20}$ –53.2 (*c* 0.9 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 2988, 2935, 1067; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (3H, s), 1.36 (3H, s), 1.45 (3H, s) and 1.55 (3H, s, $C\mathbf{H}_3$), 3.20 (1H, dd, *J* 10.1, 7.2 Hz, $C^6\mathbf{H}HI$), 3.32 (1H, dd *J* 10.1, 6.9 Hz, $C^6H\mathbf{H}I$), 3.95 (1H, td, *J* 7.0, 1.8 Hz, $C^5\mathbf{H}$), 4.30 (1H, dd, *J* 5.1, 2.5 Hz, $C^2\mathbf{H}$), 4.41 (1H, dd, *J* 7.9, 1.8 Hz, $C^4\mathbf{H}$), 4.61 (1H, dd, *J* 7.9, 2.5 Hz, $C^3\mathbf{H}$), 5.55 (1H, d, *J* 5.1 Hz, $C^1\mathbf{H}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.4 ($\mathbf{C}^6$), 24.5, 25.0, 26.0 and 26.1 ($\mathbf{C}H_3$), 69.0 ($\mathbf{C}^5$), 70.6 ($\mathbf{C}^2$), 71.2 ($\mathbf{C}^3$), 71.7 ($\mathbf{C}^4$), 96.8 ($\mathbf{C}^1$), 108.9 and 109.6 ($\mathbf{C}(CH_3)_2$); *m*/*z* (CI) 371 (MH^+, 74%), 355 (96), 313 (100); HRMS found 371.0352, $C_{12}H_{20}IO_5$ (MH^+) requires 371.0355.

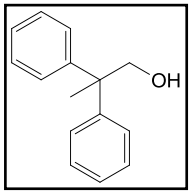
[(1*S*,2*R*,6*R*,8*R*,9*S*)-4,4,11,11-Tetramethyl-3,5,7,10,12-pentaoxatricyclo[7.3.0.0^{2,6}] dodecan-8- yl]methyl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 49:1→19:1) afforded the formate as a yellow oil: υ_{max}/cm^{-1} (DCM cast) 2989, 2937, 1722; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (3H, s), 1.35 (3H, s), 1.46 (3H, s) and 1.53 (3H, s, 4 × $C\mathbf{H}_3$), 4.02-4.08 (1H, m, $C^5\mathbf{H}$), 4.25 (1H, dd, *J* 7.9, 2.0 Hz, $C^4\mathbf{H}$), 4.27-4.39 (3H, m, $C^2\mathbf{H}$ and $C^6\mathbf{H}_2$), 4.64 (1H, dd, *J* 7.9, 2.6 Hz, $C^3\mathbf{H}$), 5.55 (1H, d, *J* 5.1 Hz, $C^1\mathbf{H}$), 8.10 (1H, s, $C\mathbf{H}O$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 24.9, 25.9 and 26.0 (4 × $\mathbf{C}H_3$),

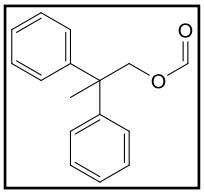
63.0 (**C**^{6}), 65.8 (**C**^{5}), 70.3 (**C**^{2}), 70.7 (**C**^{3}), 70.9 (**C**^{4}), 96.2 (**C**^{1}), 108.8 and 109.7 (2 × **C**$(CH_3)_2$), 106.9 (**C**HO); *m*/*z* (CI) 289 (MH^+, 15%), 273 (41), 231 (100); HRMS found 289.1281, $C_{13}H_{21}O_7$ (MH^+) requires 289.1287.

2,2-Diphenylpropan-1-ol



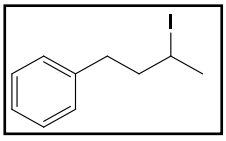
To a solution of 2,2-Diphenylpropionic acid (1.00 g, 4.42 mmol) in THF (20 mL) at 0 °C was added $LiAlH_4$ (0.25 g, 6.57 mmol) portionwise and the solution stirred at rt for 1 h. The reaction was quenched slowly with H_2O (20 mL) and stirred for a further 0.5 h. Following removal of THF *in vacuo*, the organic material was extracted with MeOH/Et_2O (1:19, 3 × 60 mL), washed with 1 M H_2SO_4 (100 mL), brine (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to afford the alcohol (0.74 g, 79%) as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3393 br, 3056, 3027, 2971, 2877, 1599, 1494, 1444; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (3H, s, C**H**$_3$), 4.12 (2H, s, C**H**$_2$), 7.21-7.38 (10H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.6 (**C**H_3), 48.8 (**C**CH_3), 70.9 (**C**H_2), 126.4, 127.7 and 128.4 (Aromatic **C**H), 146.6 (Aromatic **C**); *m*/*z* (EI) 211 (M–H, 7%), 195 (65), 101 (23), 84 (82), 83 (100); HRMS found 211.1117, $C_{15}H_{15}O$ (M–H) requires 211.1123.

2,2-Diphenylpropyl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded the formate as a pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 2971, 1724, 1496; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (3H, s, C**H**$_3$), 4.69 (2H, s, C**H**$_2$), 7.19-7.39 (10H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6 (**C**H_3), 46.5 (**C**$MePh_2$), 70.5 (**C**H_2), 126.5, 127.3 and 128.3 (Aromatic **C**H), 145.9 (Aromatic **C**), 160.9 (**C**HO); *m*/*z* (CI) 195 ($[M–CO_2H]^+$, 100%); HRMS found 195.1169, $C_{15}H_{15}$ ($[M–CO_2H]^+$) requires 195.1174.

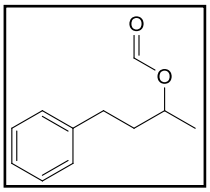
1-(3-Iodobutyl)benzene



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, hexane) afforded the iodide as a pale

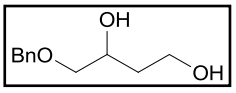
yellow oil: υ_{max}/cm^{-1} (DCM cast) 3026, 2915, 1602, 1495, 1452; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.86-1.94 (1H, dddd, *J* 14.5, 9.0, 7.0, 4.5 Hz, $CH_3CHC\mathbf{H}H$), 1.97 (3H, d, *J* 6.8 Hz, $C\mathbf{H}_3$), 2.18 (1H, dtd, *J* 14.5, 9.0, 5.1 Hz, $CH_3CHCH\mathbf{H}$), 2.72 (1H, ddd, *J* 13.7, 9.0, 7.0 Hz) and 2.88 (1H, ddd, *J* 13.7, 9.0, 5.1 Hz, $PhC\mathbf{H}_2$), 4.10-4.17 (1H, dqd, *J* 9.0, 6.8, 4.5 Hz, C**H**I), 7.21-7.26 (3H, m) and 7.29-7.34 (2H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.1 ($\mathbf{C}H_3$), 29.7 (**C**HI), 35.9 ($Ph\mathbf{C}H_2$), 44.5 ($CH_3CH\mathbf{C}H_2$), 126.2 and 128.6 (Aromatic **C**H), 140.8 (Aromatic **C**); *m*/*z* (EI) 260 (MH^+, 15%), 133 (50), 91 (100); HRMS found 260.0060, $C_{10}H_{13}I$ (MH^+) requires 260.0057.

4-Phenylbutan-2-yl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, hexane/EtOAc 49:1) afforded the formate as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 2923, 2855, 1720, 1603, 1496; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (3H, d, *J* 6.3 Hz, $C\mathbf{H}_3$), 1.81-1.90 (1H, m , $PhCH_2C\mathbf{H}H$), 1.94-2.02 (1H, m, $PhCH_2CH\mathbf{H}$), 2.64 (1H, m, PhC**H**H), 2.70 (1H, m, PhCH**H**), 5.07 (1H, m, C**H**CH_3), 7.20 (3H, m, $CH_2CC\mathbf{H}$ and $CH_2CCHCHC\mathbf{H}$), 7.30 (2H, m, $CH_2CCHC\mathbf{H}$), 8.09 (1H, s, C**H**C=O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 ($\mathbf{C}H_3$), 31.7 ($Ph\mathbf{C}H_2$), 37.6 ($PhCH_2\mathbf{C}H_2$), 70.6 (**C**HCH_3), 126.1 ($CH_2CCHCH\mathbf{C}H$), 128.4 ($CH_2C\mathbf{C}H$), 128.5 ($CH_2CCH\mathbf{C}H$), 141.3 (Aromatic **C**), 160.9 (**C**HO); *m*/*z* (EI) 132 ($[M–CO_2H_2]^+$, 35%), 117 (57), 91 (100); HRMS found 132.0935, $C_{10}H_{12}$ ($M–[CO_2H_2]^+$) requires 132.0939.

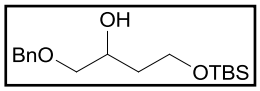
4-(Benzyloxy)butane-1,3-diol (333)[111]



To a solution of triol **331** (269 µL, 3.02 mmol) in toluene (120 mL) was added dibutyltin dimethoxide (757 µL, 3.30 mmol) and the solution distilled until the volume had halved. After cooling the resulting solution to rt, benzyl bromide (395 µL, 3.32 mmol) and tetrabutyl ammonium iodide (1.66 g, 4.49 mmol) were added successively and the solution stirred at rt for 18 h. Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 3:7) afforded diol **333** (340 mg, 58%) as a yellow solid: mpt. 74-76 °C [Lit.[128] 75-76 °C]; υ_{max}/cm^{-1} (solid) 3369 br, 2925, 2865, 1496, 1453; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.68-1.77 (2H, m, $C\mathbf{H}_2CH_2OH$),

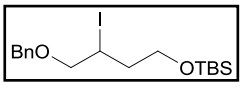
2.46 (1H, dd, *J* 6.0, 4.8 Hz, CH_2O**H**), 2.78 (1H, dd, *J*, 3.8, 0.4 Hz, CHO**H**), 3.42 (1H, dd, *J* 9.4, 7.6 Hz) and 3.53 (1H, dd, *J* 9.4, 3.5 Hz, BnOC**H**$_2$), 3.83-3.87 (2H, m, C**H**$_2$OH), 4.07-4.11 (1H, dddd, *J* 8.6, 7.6, 6.8, 3.5 Hz, C**H**OH), 4.58 (2H, s, PhC**H**$_2$), 7.31-7.39 (Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ); 34.8 (**C**H_2CH_2OH), 61.1 (**C**H_2OH), 70.4 (**C**HOH), 73.4 (Ph**C**H_2), 74.3 (BnO**C**H_2), 127.8, 127.9 and 128.5 (Aromatic **C**H), 137.8 (Aromatic **C**); *m*/*z* (CI) 197 (MH^+, 7%), 181 (6), 119 (10), 92 (17), 91 (24), 83 (100); HRMS found 197.1181, $C_{11}H_{17}O_3$ (MH^+) requires 197.1178.

1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)butan-2-ol (334)



To a solution of diol **333** (0.65 g, 3.31 mmol) and imidazole (0.25 g, 3.67 mmol) in DCM (35 mL) at 0 °C was added TBSCl (0.52 g, 3.45 mmol) and the solution stirred at rt for 5 h. H_2O (20 mL) was added and the organic material extracted with DCM (3 × 30 mL). The organic layers were combined, washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded silyl ether **334** (0.85 g, 83%) as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3464 br, 2928, 2857, 1471; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.08 (6H, s, Si(C**H**$_3$)$_2$), 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.70-1.74 (2H, m, C**H**$_2$CH$_2$OTBS), 3.20 (1H, s, O**H**), 3.44 (1H, dd, *J* 9.5, 6.8 Hz, BnOC**H**H), 3.47 (1H, dd, *J* 9.5, 4.4 Hz, BnOCH**H**), 3.80 (1H, dt, *J* 10.2, 6.0 Hz, C**H**HOTBS), 3.87 (1H, dt, *J* 10.2, 5.5 Hz, CH**H**OTBS), 4.04 (1H, m, C**H**OH), 4.57 (1H, d, *J* 12.0 Hz) and 4.59 (1H, d, *J* 12.0 Hz, PhC**H**$_2$), 7.29-7.32 (1H, m, Aromatic C**H**), 7.34-7.38 (4H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.5 (Si(**C**H_3)$_2$), 18.2 (**C**Me$_3$), 25.9 (C(**C**H_3)$_3$), 35.4 (**C**H_2CH_2OTBS), 61.5 (**C**H_2OTBS), 69.8 (**C**HOH), 73.4 (Ph**C**H_2), 74.4 (BnO**C**H_2), 127.7, 127.8 and 128.4 (Aromatic **C**H), 138.2 (Aromatic **C**); *m*/*z* (ES^+) 333 (MNa^+, 100%); HRMS found 333.1859, $C_{17}H_{30}O_3NaSi$ (MNa^+) requires 333.1862.

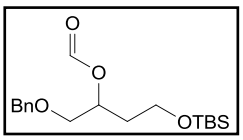
(4-(Benzyloxy)-3-iodobutoxy)(*tert*-butyl)dimethylsilane



The crude material was obtained using *Method A*. Purification by flash chromatography (SiO_2, petrol) afforded the iodide as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 2953, 2928, 2856; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.06 (3H, s) and 0.09 (3H, s, Si(C**H**$_3$)$_2$), 0.91 (9H, s, C(C**H**$_3$)$_3$), 1.95 (1H, ddt, *J* 14.6,

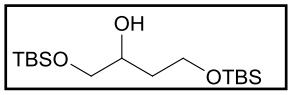
9.9, 4.5 Hz) and 2.07 (1H, dddd, *J* 14.6, 8.6, 5.8, 3.9 Hz, C**H**$_2$CH$_2$OTBS), 3.72 (1H, ddd, *J* 10.3, 8.6, 4.7 Hz, C**H**HOTBS), 3.73 (1H, dd, *J* 10.5, 6.5 Hz, BnOC**H**H), 3.78 (1H, dd, *J* 10.5, 6.0 Hz, BnOCH**H**), 3.81 (1H, ddd, *J* 10.3, 5.8, 4.3 Hz, CH**H**OTBS), 4.41 (1H, dtd, *J* 9.9, 6.2, 3.9 Hz, C**H**I), 4.61 (2H, s, C**H**$_2$Ph), 7.30-7.39 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.2 (Si(**C**H$_3$)$_2$), 18.4 (**C**Me$_3$), 26.0 (C(**C**H$_3$)$_3$), 30.5 (**C**HI), 39.4 (**C**H$_2$CH$_2$OTBS), 62.2 (**C**H$_2$OTBS), 72.9 (**C**H$_2$Ph), 75.9 (BnO**C**H$_2$), 127.7, 127.8 and 128.5 (Aromatic **C**H), 137.9 (Aromatic **C**); *m*/*z* (CI) 421 (MH$^+$, 6%), 313 (24), 187 (19), 145 (100); HRMS found 421.1066, $C_{17}H_{30}IO_2Si$ (MH$^+$) requires 421.1060.

1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)butan-2-yl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) afforded the formate as a pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 2954, 2928, 2857, 1724; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.89 (6H, s, Si(CH$_3$)$_2$), 0.90 (9H, s, C(CH$_3$)$_3$), 1.84-1.90 (2H, m, CH$_2$CH$_2$OTBS), 3.58 (1H, dd, *J* 10.8, 6.2, Hz) and 3.64 (1H, dd, *J* 10.8, 3.4 Hz, BnOCHH), 3.65-3.70 (2H, m, C**H**$_2$OTBS), 4.53 (1H, d, *J* 12.0 Hz) and 4.60 (1H, d, *J* 12.0 Hz, C**H**$_2$Ph), 5.28 (1H, m, C**H**OCHO), 7.29-7.39 (5H, m, Aromatic C**H**), 8.13 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.5 (Si(**C**H$_3$)$_2$), 18.2 (**C**Me$_3$), 25.9 (C(**C**H$_3$)$_3$), 33.7 (**C**H$_2$CH$_2$OTBS), 58.8 (**C**H$_2$OTBS), 70.7 (**C**HOCHO), 71.2 (BnO**C**H$_2$), 73.2 (**C**H$_2$Ph), 127.7, 127.8 and 128.4 (Aromatic **C**H), 137.8 (Aromatic **C**), 161.0 (**C**HO); *m*/*z* (CI) 339 (MH$^+$, 5%), 231 (26), 187 (17), 145 (100); HRMS found 339.1983, $C_{18}H_{31}O_4Si$ (MH$^+$) requires 339.1992.

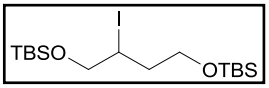
1,4-Bis(*tert*-butyldimethylsilyloxy)butan-2-ol (332)



To a solution of triol **331** (0.42 mL, 4.71 mmol) and imidazole (706 mg, 10.4 mmol) in DCM (45 mL) at 0 °C was added TBSCl (1.49 g, 9.89 mmol) and solution stirred for 18 h at rt. H_2O (30 mL) was added and the organic material extracted with DCM (3 × 40 mL), washed with brine (30 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 19:1) afforded alcohol **332** (0.96 g, 61%) as a colourless

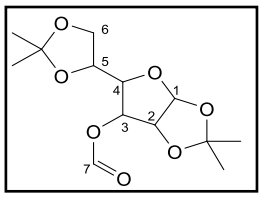
oil: υ_{max}/cm^{-1} (neat) 3471 br, 2954, 2929, 2858; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (12H, s, 2 × Si(C**H**$_3$)$_2$), 0.91 (18H, s, 2 × C(C**H**$_3$)$_3$), 1.64-1.72 (2H, m, C**H**$_2$CH$_2$OTBS), 3.01 (1H, d, *J* 3.0 Hz, O**H**), 3.53 (1H, dd, *J* 9.9, 6.4 Hz) and 3.61 (1H, dd, *J* 9.9, 5.0 Hz, TBSOC**H**$_2$CH), 3.79-3.87 (3H, m, CH$_2$C**H**$_2$OTBS and C**H**OH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ -5.5 and -5.4 (2 × Si(**C**H$_3$)$_2$), 18.2 and 18.3 (2 × **C**Me$_3$), 25.9 (C(**C**H$_3$)$_3$), 35.4 (**C**H$_2$CH$_2$OTBS), 61.2 (CH$_2$**C**H$_2$OTBS), 67.2 (TBSO**C**H$_2$CH), 70.9 (**C**HOH); *m*/*z* (ES^-) 333 ($[M-H]^+$, 100%); HRMS found 333.2278, $C_{16}H_{37}O_3Si_2$ ($[M-H]^+$) requires 333.2281.

1,4-Bis(*tert*-butyldimethylsilyloxy)-2-iodobutane



The crude material was obtained using *Method A.* Purification by flash chromatography (Al_2O_3, petrol) afforded the iodide as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2954, 2929, 2857; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.08 (3H, s), 0.08 (3H, s), 0.09 (3H, s) and 0.10 (3H, s, 2 × Si(C**H**$_3$)$_2$), 0.91 (9H, s) and 0.92 (9H, s, 2 × C(C**H**$_3$)$_3$), 1.87 (1H, dddd, *J* 14.6, 10.2, 4.9, 4.1 Hz) and 2.10 (1H, dddd, *J* 14.6, 8.6, 6.0, 3.6 Hz, CHIC**H**$_2$CH$_2$OTBS), 3.71 (1H, ddd, *J* 10.3, 8.6, 4.9 Hz, CHICH$_2$C**H**HOTBS), 3.80 (1H, dd, *J* 10.8, 7.3 Hz, CHIC**H**HOTBS), 3.82 (1H, ddd, *J* 10.3, 6.0, 4.1 Hz, CHICH$_2$CH**H**OTBS), 3.91 (1H, dd, *J* 10.8, 5.4 Hz, CHICH**H**OTBS), 4.26 (1H, dddd, *J* 10.2, 7.3, 5.4, 3.6 Hz, C**H**I); ^{13}C NMR ($CDCl_3$, 150 MHz) δ –5.3, –5.3 and –5.2 (2 × Si(**C**H$_3$)$_2$), 18.3 and 18.3 (2 × **C**Me$_3$), 25.9 and 25.9 (2 × C(**C**H$_3$)$_3$), 34.5 (**C**HI), 39.0 (CHI**C**H$_2$CH$_2$OTBS), 62.4 (CHICH$_2$**C**H$_2$OTBS), 69.2 (CHI**C**H$_2$OTBS); *m*/*z* (CI) 445 (MH^+, 100%), 313 (20); HRMS found 445.1452, $C_{16}H_{38}IO_2Si_2$ (MH^+) requires 445.1450.

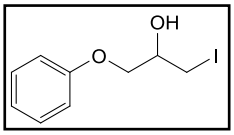
5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-6-yl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 17:3) afforded the formate as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 2988, 2938, 1729; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (6H, s), 1.43 (3H, s) and 1.54 (3H, s, C**H**$_3$), 4.04 (1H, dd, *J* 8.6, 4.0 Hz) and 4.11 (1H, dd, *J* 8.6, 5.4 Hz, C^6**H**$_2$), 4.18-4.28 (2H, m,

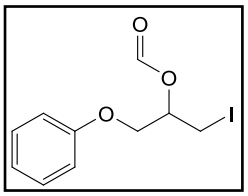
C^4**H** and C^5**H**), 4.55 (1H, d, *J* 3.7 Hz, C^2**H**), 5.36 (1H, d, *J* 2.3 Hz, C^3**H**), 5.90 (1H, d, *J* 3.7 Hz, C^1**H**), 8.15 (1H, s, C^7**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3, 26.3, 26.8 and 27.1 (**C**H_3), 67.5 (**C**^{6}), 72.4 (**C**^{4}), 76.0 (**C**^{3}), 79.8 (**C**^{5}), 83.4 (**C**^{2}), 105.2 (one of **C**$(CH_3)_2$), 109.7 (**C**^{1}), 112.6 (one of **C**$(CH_3)_2$), 159.7 (**C**^{7}); *m*/*z* (ES$^+$) 289 (MH^+, 100%); HRMS found 289.1277, $C_{13}H_{21}O_7$ (MH^+) requires 289.1287.

1-Iodo-3-phenoxypropan-2-ol (336)



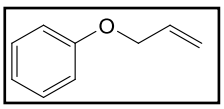
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded iodide **336** as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3390 br, 3038, 2926, 1598, 1597, 1493; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20-2.80 (1H, br s, O**H**), 3.41 (1H, dd, *J* 10.3, 5.7 Hz) and 3.49 (1H, dd, *J* 10.3, 5.3 Hz, C**H**$_2$I), 4.01 (1H, qd, *J* 5.6, 4.5 Hz, C**H**OH), 4.06 (1H, dd, *J* 9.4, 4.5, OC**H**H), 4.11 (1H, dd, *J* 9,4, 5.7 Hz, OCH**H**), 6.91-6.95 (2H, m, OCC**H**), 6.98-7.00 (1H, m, OCCHCHC**H**), 7.28-7.35 (2H, m, OCCHC**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.3 (**C**H_2I), 69.7 (**C**HOH), 70.4 (O**C**H_2), 114.7 (OC**C**H), 121.6 (OCCHCH**C**H), 129.7 (OCCH**C**H), 158.2 (Aromatic **C**); *m*/*z* (EI) 278 (M^+, 98%), 133 (34), 107 (99), 94 (100); HRMS found 277.9788, $C_9H_{11}O_2I$ (M^+) requires 277.9798.

3-Iodo-1-phenoxypropan-2-yl formate (338)



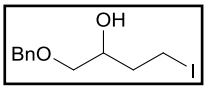
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 49:1→19:1) afforded iodide **338** as a pale yellow oil: υ_{max}/cm^{-1} (DCM cast) 3041, 2927, 1721, 1599, 1588, 1495; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.49 (1H, dd, *J* 10.7, 5.5 Hz) and 3.57 (1H, dd, *J* 10.7, 6.0 Hz, C**H**$_2$I), 4.17 (1H, dd, *J* 10.3, 4.9 Hz) and 4.26 (1H, dd, *J* 10.3, 5.0 Hz, OC**H**$_2$), 5.23-5.29 (1H, m, OC**H**), 6.93 (2H, m, OCC**H**), 7.00 (1H, m, OCCHCHC**H**), 7.32 (2H, m, OCCHC**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 2.3 (**C**H_2I), 67.8 (O**C**H_2), 70.7 (O**C**H), 114.6 (OC**C**H), 121.6 (OCCHCH**C**H), 129.6 (OCCH**C**H), 158.0 (C**H**O), 159.8 (Aromatic **C**); *m*/*z* (EI) 306 (M^+, 6%), 213 (100); HRMS found 305.9748, $C_{10}H_{11}O_3I$ (M^+) requires 305.9747.

1-(Allyloxy)benzene (337)



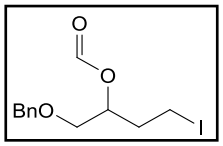
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 49:1) afforded allyl ether **337** as a colourless liquid: υ_{max}/cm^{-1} (DCM cast) 2922, 2853, 1729, 1599, 1496; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.55 (2H, dt, *J* 5.3, 1.5 Hz, OC**H**$_2$), 5.27-5.31 (1H, m, CH=C**H**H), 5.40-5.46 (1H, m, CH=CH**H**), 6.03-6.13 (1H, m, C**H**=CH_2), 6.91-6.98 (3H, m, OCC**H** and OCCHCHC**H**), 7.27-7.33 (2H, m, OCCHC**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 68.8 (O**C**H$_2$), 114.8 (OCCHCH**C**H), 117.7 (CH=**C**H$_2$), 120.9 (OC**C**H), 129.5 (OCCH**C**H), 133.4 (**C**H=CH$_2$), 158.7 (Aromatic **C**); *m*/*z* (EI) 134 (M^+, 100%); HRMS found 134.0725, $C_9H_{10}O$ (M^+) requires 134.0726.

1-(Benzyloxy)-4-iodobutan-2-ol (339)



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 9:1→17:3) afforded iodide **339** as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3425 br, 3030, 2859, 1496, 1453; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.88-2.04 (2H, m, C**H**$_2$CH$_2$I), 2.28-2.52 (1H, br s, O**H**), 3.30-3.35 (2H, m, C**H**$_2$I), 3.39 (1H, dd, *J* 9.4, 7.2 Hz, BnOC**H**H), 3.53 (1H, dd, *J* 9.4, 3.2 Hz, BnOCH**H**), 3.90-3.99 (1H, m, C**H**(OH)), 4.57 (2H, s, PhC**H**$_2$), 7.30-7.41 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.45 (**C**H$_2$I), 37.0 (**C**H$_2$CH$_2$I), 70.4 (**C**H(OH)), 73.5 (Ph**C**H$_2$), 73.8 (BnO**C**H$_2$), 127.9, 128.0 and 128.6 (Aromatic **C**H), 137.8 (Aromatic **C**); *m*/*z* (EI) 306 (M^+, 17%), 199 (12), 181 (17), 92 (17), 91 (100); HRMS found 306.0120, $C_{11}H_{15}O_2I$ (M^+) requires 306.0111.

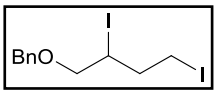
1-(Benzyloxy)-4-iodobutan-2-yl formate



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1→9:1) afforded the formate as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3030, 2919, 2862, 1718; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15-2.34 (2H, m, C**H**$_2$CH$_2$I), 3.10-3.24 (2H, m, C**H**$_2$I), 3.58-3.60 (2H, m, BnOC**H**$_2$), 4.52 (1H, d, *J* 12.0 Hz, PhC**H**H), 4.56 (1H, d, *J* 12.0 Hz, PhCH**H**), 5.17-5.24 (1H, m, C**H**OC=O), 7.29-7.40 (5H, m, Aromatic C**H**),

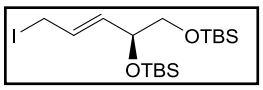
8.13 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.1 (**C**H_2I), 34.8 (**C**H_2CH_2I), 70.2 (BnO**C**H_2), 72.9 (**C**HOC=O), 73.4 (Ph**C**H_2), 127.8, 128.0 and 128.6 (Aromatic **C**H), 137.6 (Aromatic **C**), 160.6 (O=**C**H); *m*/*z* (CI) 335 (MH^+, 30%), 334 (33) 331 (24), 227 (36), 181 (46), 91 (100); HRMS found 335.0135, $C_{12}H_{16}O_3I$ (MH^+) requires 335.0144.

1-((2,4-Diiodobutoxy)methyl)benzene



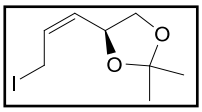
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol→petrol/EtOAc 19:1) afforded the diiodide as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3029, 2918, 2850; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19-2.39 (2H, m, C**H**$_2$CH$_2$I), 3.24 (1H, ddd, *J* 9.9, 8.5, 7.1 Hz, C**H**HI), 3.40 (1H, ddd, *J* 9.9, 7.1, 4.8 Hz, CH**H**I), 3.73 (1H, dd, *J* 10.4, 7.4 Hz, BnOC**H**H), 3.80 (1H, dd, *J* 10.4, 5.3 Hz, BnOCH**H**), 4.26-4.34 (1H, m, C**H**I), 4.60 (2H, s, PhC**H**$_2$), 7.30-7.41 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.7 (**C**H_2I), 32.8 (**C**HI), 39.8 (**C**H_2CH_2I), 73.1 (Ph**C**H_2), 75.1 (BnO**C**H_2), 127.8, 128.0 and 128.6 (Aromatic **C**H), 137.7 (Aromatic **C**); *m*/*z* (EI) 416 (M^+, 38%), 413 (35), 309 (44), 290 (35), 289 (43), 259 (43), 181 (35), 131 (32), 91 (100); HRMS found 415.9119, $C_{11}H_{14}OI_2$ (M^+) requires 415.9129.

(*S*,*E*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-1-iodopent-2-ene



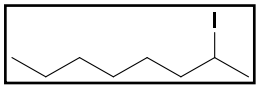
The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol) afforded the iodide as a colourless oil: $[\alpha]_D^{21} = -17.0$ (*c* 0.70 in $CHCl_3$); υ_{max}/cm^{-1} (DCM cast) 2954, 2928, 2857; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.06 (6H, s) and 0.08 (6H, s, 2 × Si(C**H**$_3$)$_2$), 0.90 (9H, s) and 0.91 (9H, s, 2 × C(C**H**$_3$)$_3$), 3.43 (1H, dd, *J* 10.0, 6.2 Hz) and 3.54 (1H, dd, *J* 10.0, 6.3 Hz, OC**H**$_2$), 3.89 (1H, dddd, *J* 10.6, 8.2, 1.0, 0.6 Hz) and 3.92 (1H, dddd, *J* 10.6, 8.0, 1.0, 0.6 Hz, C**H**$_2$I), 4.16 (1H, m, OC**H**), 5.74 (1H, ddt, *J* 15.1, 5.4, 1.0 Hz, ICH$_2$CH=C**H**), 5.96 (1H, dtd, *J* 15.1, 8.1, 1.4 Hz, ICH$_2$C**H**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.6 and –4.5 (2 × Si(**C**H$_3$)$_2$), 5.5 (**C**H$_2$I), 18.4 and 18.5 (2 × **C**(CH$_3$)$_3$), 26.0 and 26.0 (2 × C(**C**H$_3$)$_3$), 67.7 (TBSO**C**H$_2$), 73.1 (TBSO**C**H), 128.4 (BrCH$_2$**C**H=CH), 134.7 (BrCH$_2$CH=**C**H); *m*/*z* (EI) 399 ([M–^{t}Bu]$^+$, 30%), 184 (24), 147 (100); HRMS found 399.0671, $C_{13}H_{28}O_2Si_2I$ ([M–^{t}Bu]$^+$) requires 399.0667.

(*S*,*Z*)-4-(3-Iodoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol/EtOAc 97:3) afforded the iodide as a colourless oil: $[\alpha]_D^{20} = -163.2$ (*c* 0.50 in $CHCl_3$); υ_{max}/cm^{-1} (neat) 2985, 2932, 2868; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.43 (3H, s) and 1.45 (3H, s, $C(C\mathbf{H}_3)_2$), 3.60 (1H, t, *J* 7.9 Hz, OC**H**H), 3.88 (1H, dd, *J* 9.8, 8.1 Hz) and 4.04 (1H, td, *J* 9.8, 0.9 Hz, $C\mathbf{H}_2I$), 4.21 (1H, dd, *J* 8.3, 6.2 Hz, OCH**H**), 4.91 (1H, m, OC**H**), 5.47 (1H, dd, *J* 10.6, 8.3 Hz, $ICH_2CH{=}C\mathbf{H}$), 5.97 (1H, m, $ICH_2C\mathbf{H}$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −1.7 ($\mathbf{C}H_2I$), 25.9 and 26.7 ($C(\mathbf{C}H_3)_2$), 68.5 ($O\mathbf{C}H_2$), 71.0 (O**C**H), 109.6 ($\mathbf{C}Me_2$), 130.7 ($ICH_2CH{=}\mathbf{C}H$), 130.9 ($ICH_2\mathbf{C}H$); *m*/*z* (CI) 286 (MNH_4^+, 15%), 269 (52), 228 (100), 209 (32), 141 (21); HRMS found 269.0033, $C_8H_{14}O_2I$ (MH^+) requires 269.0033.

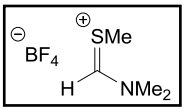
2-Iodooctane (341)



The crude material was obtained using *Method A.* Purification by flash chromatography (SiO_2, petrol) afforded iodide **341** as a colourless oil: $[\alpha]_D^{24}$ (toluene) = +4.8 (*c* 3.7 in $CHCl_3$), $[\alpha]_D^{24}$ (THF) = +0.1 (*c* 3.7 in $CHCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ cast) 2956, 2924, 2854; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.90 (3H, t, *J* 7.1 Hz, $C\mathbf{H}_3CH_2$), 1.26-1.53(8H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$), 1.59-1.65 (1H, dddd, *J* 5.1, 9.9, 10.4, 14.3 Hz) and 1.82-1.89 (1H, dddd, *J* 4.7, 8.4, 9.9, 14.3 Hz, $C\mathbf{H}_2CHI$), 1.94 (3H, d, *J* 6.8 Hz, $C\mathbf{H}_3CHI$), 4.20 (1H, dqd, *J* 5.1, 6.8, 8.4 Hz, C**H**I); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1 ($\mathbf{C}H_3CH_2$), 22.6 and 28.4 (2 of $CH_3\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2$), 29.0 ($\mathbf{C}H_3CHI$), 29.7 (1 of $CH_3\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2$), 31.0 (**C**HI), 31.7 (1 of $CH_3\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2\mathbf{C}H_2$), 42.9 ($\mathbf{C}H_2CHI$); *m*/*z* (EI) 240 ($M^+$, 15%), 219 (37), 169 (28), 155 (45), 128 (100); HRMS found 240.0376, $C_8H_{17}I$ (M^+) requires 240.0370.

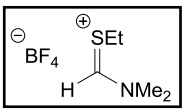
Conversion of alcohols to 1-phenyltetrazol-5-yl sulphides

N,*N*,*N*-Trimethylmethanethioamide tetrafluoroborate (342)



To a solution of $Me_3O^+BF_4^-$ (5.73 g, 38.7 mmol) in DCM (70 mL) was added $HCSNMe_2$ (3.00 mL, 35.2 mmol) and the solution stirred at rt for 18 h. The mixture was concentrated *in vacuo* to remove half of its volume and then transferred dropwise into Et_2O (200 mL); the solution was then left in the fridge for 2 h. The resulting precipitate was collected by filtration under argon, washed with cold Et_2O (2 × 30 mL) and dried *in vacuo* for 10 min to give salt **342** (6.25 g, 93%) as a white crystalline solid which was stored in a freezer under argon: mpt. 24-26 ºC; υ_{max}/cm^{-1} (solid) 3083, 1647, 1627, 1428; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.93 (3H, s, SC**H**$_3$), 3.41 (3H, s) and 3.73 (3H, s, N(C**H**$_3$)$_2$), 9.62 (1H, s, C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.1 (S**C**H$_3$), 42.3 and 49.5 (N(**C**H$_3$)$_2$), 184.5 (**C**=SMe); *m*/*z* (CI) 104 ([M–BF_4]$^+$, 100%), 90 (26); HRMS found 104.0539, $C_4H_{10}NS$ ([M–BF_4]$^+$) requires 104.0534.

N-Ethyl-*N*,*N*-dimethylmethanethioamide tetrafluoroborate (343)



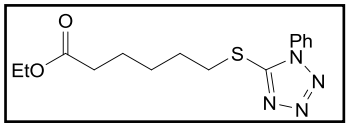
To a solution of $Et_3O^+BF_4^-$ (5.57 g, 29.3 mmol) in DCM (50 mL) was added $HCSNMe_2$ (2.30 mL, 26.7 mmol) and the solution stirred at rt for 18 h. The mixture was concentrated *in vacuo* to remove half of its volume and then transferred dropwise into Et_2O (100 mL); the solution was then left in the fridge for 2 h. The resulting precipitate was collected by filtration under argon, washed with cold Et_2O (2 × 25 mL) and dried *in vacuo* for 10 min to give salt **343** (5.26 g, 96%) as a white crystalline solid which was stored in a freezer under argon: mpt. 20-21 ºC; υ_{max}/cm^{-1} (solid) 3076, 1650, 1634, 1463; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51 (3H, t, *J* 7.5 Hz, $CH_2C\mathbf{H}_3$), 3.40 (3H, s, $NC\mathbf{H}_3CH_3$), 3.41 (2H, q, *J* 7.5 Hz, C**H**$_2$), 3.73 (3H, s, $NCH_3C\mathbf{H}_3$), 9.57 (1H, s, C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.6 ($CH_2\mathbf{C}H_3$), 30.1 (**C**H$_2$), 42.4 and 49.4 (N(**C**H$_3$)$_2$), 183.1 (**C**=SEt); *m*/*z* (CI) 118 ([M–BF_4]$^+$, 100%), 90 (48); HRMS found 118.0686, $C_5H_{12}NS$ ([M–BF_4]$^+$) requires 118.0691.

General procedure for C-S bond formation reactions – *Method B*

To a solution of alcohol (1.0 equiv.) in toluene (0.4-0.5M substrate concentration) was added salt **343** (1.5 equiv.), imidazole (1.0 equiv. or 5.0 equiv. for acid sensitive substrates) and thiol (2.0 equiv. or 1.2 equiv. for allylic and benzylic alcohols) and the mixture heated to 90 °C. Upon completion (reaction monitored by TLC or ^{1}H NMR analysis), the solvent was removed *in vacuo* to give the crude product. Purification by flash chromatography (as described) afforded pure products.

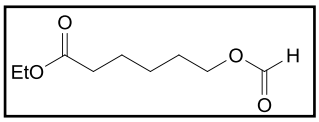
For yields and reaction times, please refer to Table 9, section 4.2.1.2

Ethyl 6-(1-phenyl-1H-tetrazol-5-ylthio)hexanoate (346)



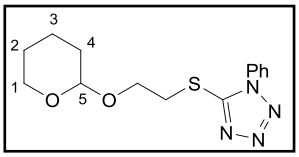
The crude material was obtained using *Method B*. Purification by flash chromatography (Al_2O_3, petrol/EtOAc 19:1→9:1) gave sulfide **346** as a yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2980, 2937, 2865, 1729, 1597, 1500; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24 (3H, t, *J* 7.3 Hz, C**H**$_3$), 1.48 (2H, app. quin, *J* 7.5 Hz, C**H**$_2$CH$_2$CH$_2$S), 1.67 (2H, app. quin, *J* 7.5 Hz, C**H**$_2$CH$_2$C=O), 1.85 (2H, app. quin, *J* 7.5 Hz, C**H**$_2$CH$_2$S), 2.30 (2H, t, *J* 7.5 Hz, C**H**$_2$C=O), 3.39 (2H, t, *J* 7.4 Hz, C**H**$_2$S), 4.11 (2H, q, *J* 7.3 Hz, C**H**$_2$CH$_3$), 7.51-7.59 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.4 (**C**H$_3$), 24.4 (**C**H$_2$CH$_2$C=O), 28.2 (**C**H$_2$CH$_2$CH$_2$S), 28.9 (**C**H$_2$CH$_2$S), 33.2 (**C**H$_2$S), 34.2 (**C**H$_2$C=O), 60.4 (**C**H$_2$CH$_3$), 124.0, 129.9 and 130.2 (Aromatic **C**H), 133.8 (Aromatic **C**), 154.5 (N**C**S), 173.6 (**C**=O); *m*/*z* (CI) 321 (MH^+, 100%), 275 (41), 119 (55); HRMS found 321.1379, $C_{15}H_{21}N_4O_2S$ (MH^+) requires 321.1385.

Ethyl 6-(formyloxy)hexanoate



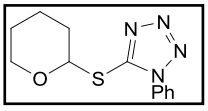
The crude material was obtained using *Method B*. Purification by flash chromatography (Al_2O_3, petrol→petrol/EtOAc 19:1) gave the formate as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 2931, 2869, 1730, 1597; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.24 (3H, t, *J* 7.1 Hz, C**H**$_3$), 1.36-1.42 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.61-1.70 (4H, m, C**H**$_2$CH$_2$O and C**H**$_2$CH$_2$C=O), 2.30 (2H, t, *J* 7.4 Hz, C**H**$_2$C=O), 4.11 (2H, q, *J* 7.1 Hz, C**H**$_2$CH$_3$), 4.15 (2H, t, *J* 6.7 Hz, C**H**$_2$O), 8.04 (1H, s, C**H**O); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.3 (**C**H$_3$), 24.6 (**C**H$_2$CH$_2$C=O), 25.5 (**C**H$_2$CH$_2$CH$_2$O), 28.3 (**C**H$_2$CH$_2$O), 34.2 (**C**H$_2$C=O), 60.4 (**C**H$_2$CH$_3$), 63.8 (**C**H$_2$O), 161.3 (**C**HO), 173.6 (**C**=O); *m*/*z* (CI) 189 (MH^+, 8%), 143 (100); HRMS found 189.1119, $C_9H_{17}O_4$ (MH^+) requires 189.1127.

1-Phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-tetrazole (349)



The crude material was obtained using *Method B*. Purification by flash chromatography (Al_2O_3, petrol/EtOAc 9:1→4:1) gave sulfide **349** as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 2942, 2871, 1597, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.45-1.60 (4H, m, C^2**H**H, C^3**H**H and C^4**H**$_2$), 1.65-1.72 (1H, m, C^{2}H**H**), 1.73-1.80 (1H, m, C^{3}H**H**), 3.49 (1H, m, C^1**H**H), 3.61 (1H, dt, *J* 13.6, 5.9 Hz) and 3.66 (1H, dt, *J* 13.6, 5.9 Hz, OCH$_2$C**H**$_2$S), 3.80-3.85 (2H, m, C^{1}H**H** and OC**H**HCH$_2$S), 4.08 (1H, dt, *J* 10.7, 5.9 Hz, OCH**H**CH$_2$S), 4.63 (1H, dd, *J* 4.1, 2.9 Hz, C^5**H**), 7.51-7.59 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.5 (**C**^{3}), 25.4 (**C**^{4}), 30.5 (**C**^{2}), 33.6 (OCH$_2$**C**H$_2$S), 62.5 (**C**^{1}), 65.6 (O**C**H$_2$CH$_2$S), 99.1 (**C**^{5}), 124.0, 129.9 and 130.3 (Aromatic **C**H), 133.8 (Aromatic **C**), 154.4 (S**C**N); *m*/*z* (ES^+) 329 (MNa^+, 80%), 301 (31), 223 (100); HRMS found 329.1052, $C_{14}H_{18}N_4O_2NaS$ (MNa^+) requires 329.1048.

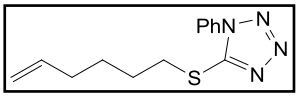
1-Phenyl-5-(tetrahydro-2H-pyran-2-ylthio)-1H-tetrazole (350)



The crude material was obtained using *Method B*. Purification by flash chromatography (Al_2O_3, petrol → petrol/EtOAc 19:1) gave tetrazole **350** as a white solid: mpt. 69-71 ºC; υ_{max}/cm^{-1} (solid) 2966, 2941, 2851, 1595,

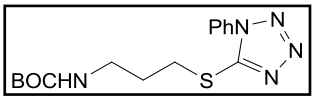
1498; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.64-1.71 (1H, m, OCH_2CHH), 1.73-1.83 (2H, m, $SCHCH_2CHH$ and OCH_2CHH), 2.04 (1H, m, $SCHCHH$), 2.11-2.20 (1H, m, $SCHCH_2CHH$), 2.36 (1H, dddd, *J* 13.1 11.8, 10.1, 4.2 Hz, $SCHCHH$), 3.80 (1H, td, *J* 11.5, 2.7 Hz) and 4.16 (1H, m, OCH_2), 5.98 (1H, dd, *J* 10.1, 2.8 Hz, $OCHS$), 7.48-7.57 (3H, m) and 7.90-7.93 (2H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.3 ($SCHCH_2CH_2$), 24.8 (OCH_2CH_2), 29.1 ($SCHCH_2$), 68.5 (OCH_2), 83.5 ($OCHS$), 124.2, 129.4 and 129.8 (Aromatic **C**H), 134.6 (Aromatic **C**), 163.7 (S**C**N); *m*/*z* (CI) 263 (MH^+, 100%), 179 (100), 85 (23); HRMS found 263.0958, $C_{12}H_{15}ON_4S$ (MH^+) requires 263.0967.

5-(Hex-5-enylthio)-1-phenyl-1H-tetrazole



The crude material was obtained using *Method B.* Purification by flash chromatography (Al_2O_3, petrol→petrol/EtOAc 19:1) gave the sulfide as a colourless oil: υ_{max}/cm^{-1} (DCM cast) 3071, 2927, 2856, 2640, 1597, 1499; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.54 (2H, app. quin, *J* 7.4 Hz, $CH_2CH_2CH=CH_2$), 1.83 (2H, app. quin, *J* 7.4 Hz, CH_2CH_2S), 2.08 (2H, q, *J* 7.0 Hz, $CH_2CH=CH_2$), 3.39 (2H, t, *J* 7.4 Hz, CH_2S), 4.95 (1H, d, *J* 10.0 Hz) and 5.00 (1H, d, *J* 17.1 Hz, CH_2=CH), 5.77 (1H, ddd, *J* 17.1, 10.0, 7.0 Hz, CH_2=C**H**), 7.50-7.59 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.9 ($CH_2CH_2CH=CH_2$), 28.6 (CH_2CH_2S), 33.2 (CH_2S), 33.3 ($CH_2CH=CH_2$), 115.2 (CH_2=CH), 123.9, 130.0 and 130.2 (Aromatic **C**H), 133.8 (Aromatic **C**), 138.1 (CH_2=**C**H), 154.6 (N**C**S); *m*/*z* (CI) 261 (MH^+, 100%), 207 (28); HRMS found 261.1165, $C_{13}H_{17}N_4S$ (MH^+) requires 261.1174.

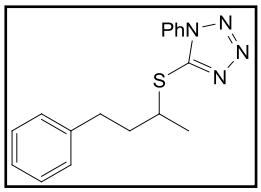
***tert*-Butyl 3-(1-phenyl-1H-tetrazol-5-ylthio)propylcarbamate**



The crude material was obtained using *Method B.* Purification by flash chromatography (Al_2O_3, petrol/EtOAc 9:1→17:3) gave the sulfide as a cloudy yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3342 br, 2978, 2929, 1696, 1597, 1500; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.43 (9H, s, $C(CH_3)_3$), 2.00-2.07 (2H, m, NCH_2CH_2), 3.22-3.30 (2H, m, CH_2N), 3.40-3.45 (2H, td, *J* 6.9, 2.0 Hz, CH_2S), 4.81-5.00 (1H, br s, N**H**), 7.51-7.60 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.5 ($C(CH_3)_3$), 29.8 (NCH_2CH_2), 30.6 (CH_2S), 38.9 (CH_2N),

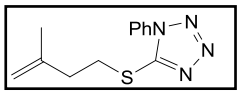
79.5 (**C**Me_3), 124.0, 129.9 and 130.3 (Aromatic **C**H), 133,7 (Aromatic **C**), 154.5 (S**C**N), 156.2 (**C**=O); *m*/*z* (EI) 335 (M^+, 8%), 279 (100); HRMS found 335.1420, $C_{15}H_{21}N_5O_2S$ (M^+) requires 335.1416.

1-Phenyl-5-(4-phenylbutan-2-ylthio)-1H-tetrazole



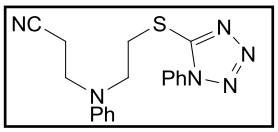
The crude material was obtained using *Method B*. Purification by flash chromatography (SiO_2, petrol → petrol/EtOAc 24:1) gave the sulfide as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3063, 3027, 2926, 2859, 1597, 1499, 1455, 1387; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.56 (3H, d, *J* 6.8 Hz, C**H**$_3$), 2.02 (1H, ddt, *J* 13.7, 9.5, 6.8 Hz) and 2.14 (1H, ddt, *J* 13.7, 9.5, 6.8 Hz, SCHC**H**$_2$), 2.72-2.83 (2H, m, PhC**H**$_2$), 4.07 (1H, sext., *J* 6.8 Hz, SC**H**), 7.15-7.21 (3H, m), 7.25-7.30 (2H, m) and 7.51-7.60 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6 (**C**H$_3$), 33.3 (Ph**C**H$_2$), 38.3 (SCH**C**H$_2$), 44.5 (S**C**H), 124.2, 126.3, 128.5, 128.6, 129.9 and 130.2 (Aromatic **C**H), 133.8 and 141.0 (Aromatic **C**), 154.0 (S**C**N); *m*/*z* (CI) 311 (MH^+, 100%), 119 (58); HRMS found 311.1327, $C_{17}H_{19}N_4S$ (MH^+) requires 311.1330.

5-(3-Methylbut-3-enylthio)-1-phenyl-1H-tetrazole



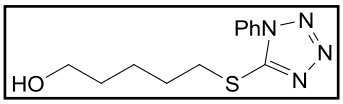
The crude material was obtained using *Method B*. Purification by flash chromatography (SiO_2, petrol → petrol/EtOAc 24:1) gave the sulfide as a pale yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3078, 2970, 2937, 1649, 1597, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.77 (3H, s, C**H**$_3$), 2.53 (2H, t, *J* 7.5 Hz, C**H**$_2$CH$_2$S), 3.53 (2H, t, *J* 7.3 Hz, CH$_2$C**H**$_2$S), 4.77 (1H, s) and 4.83 (1H, s, C**H**$_2$=C), 7.51-7.59 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.2 (**C**H$_3$), 31.5 (CH$_2$**C**H$_2$S), 37.0 (**C**H$_2$CH$_2$S), 112.6 (**C**H$_2$=C), 124.0, 129.9 and 130.2 (Aromatic **C**H), 133.8 (Aromatic **C**), 142.6 (CH$_2$=**C**), 154.5 (S**C**N); *m*/*z* (EI) 246 (M^+, 40%), 159 (45), 135 (32), 85 (100); HRMS found 246.0935, $C_{12}H_{14}N_4S$ (M^+) requires 246.0939.

3-(Phenyl(2-(1-phenyl-1H-tetrazol-5-ylthio)ethyl)amino)propanenitrile



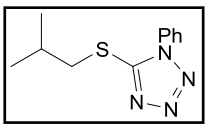
The crude material was obtained using *Method B*; in addition, an extra 1.0 equiv. imidazole (2.0 equiv. in total) was added to ensure reaction completion. Purification by flash chromatography (SiO_2, petrol/EtOAc 17:3→1:4) gave the sulfide as a thick colourless oil: υ_{max}/cm^{-1} (neat) 3063, 2932, 2248, 1693, 1597, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.65 (2H, t, *J* 6.8 Hz, CNC**H**$_2$), 3.53 (2H, t, *J* 7.2 Hz, SC**H**$_2$), 3.77 (2H, t, *J* 6.8 Hz, CNCH$_2$C**H**$_2$), 3.89 (2H, t, *J* 7.2 Hz, SCH$_2$C**H**$_2$), 6.80-6.84 (3H, m), 7.27-7.32 (2H, m) and 7.53-7.60 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.3 (CN**C**H$_2$), 30.1 (S**C**H$_2$), 47.6 (CNCH$_2$**C**H$_2$), 50.9 (SCH$_2$**C**H$_2$), 113.2 (Aromatic **C**H), 118.4 (**C**N), 118.7, 123.9, 130.0, 130.0 and 130.4 (Aromatic **C**H), 133.6 (SCN**C**), 145.7 (CH$_2$N**C**), 154.0 (S**C**N), ; *m*/*z* (ES^+) 373 (MNa^+, 100%); HRMS found 373.1211, $C_{18}H_{18}N_6NaS$ (MNa^+) requires 373.1211.

5-(1-Phenyl-1H-tetrazol-5-ylthio)pentan-1-ol (353)



The crude material was obtained using *Method B*. Purification by flash chromatography (SiO_2, petrol/EtOAc 7:3→1:1) gave sulfide **353** as a colourless oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3414 br, 2941, 2865, 1597, 1500; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.50-1.58 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.59-1.65 (2H, m, C**H**$_2$CH$_2$O), 1.84-1.91 (2H, quin., *J* 7.3 Hz, C**H**$_2$CH$_2$S), 3.40 (2H, t, *J* 7.3 Hz, C**H**$_2$S), 3.66 (2H, t, *J* 6.3 Hz, C**H**$_2$O), 7.51-7.60 (5H, m, Aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.0 (**C**H$_2$CH$_2$CH$_2$O), 29.0 (**C**H$_2$CH$_2$S), 32.1 (**C**H$_2$CH$_2$O), 33.3 (**C**H$_2$S), 62.7 (**C**H$_2$O), 124.0, 129.9 and 130.0 (Aromatic **C**H), 133.8 (Aromatic **C**), 154.5 (S**C**N); *m*/*z* (CI) 265 (MH^+, 100%); HRMS found 265.1114, $C_{12}H_{17}ON_4S$ (MH^+) requires 265.1123.

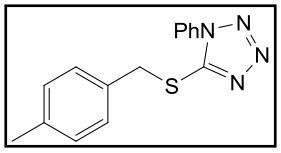
5-(Isobutylthio)-1-phenyl-1H-tetrazole



The crude material was obtained using *Method B*. Purification by flash chromatography (SiO_2, petrol → petrol/Et_2O 19:1) gave the sulfide as a colourless oil: υ_{max}/cm^{-1} (neat) 2960, 2929, 2871, 1597, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.05 (6H, d, *J* 6.8 Hz, CH(C**H**$_3$)$_2$), 2.10 (1H, non, *J* 6.8 Hz, C**H**(CH$_3$)$_2$), 3.31 (2H, d, *J* 6.8 Hz, C**H**$_2$), 7.52-7.60 (5H, m, aromatic C**H**); ^{13}C NMR

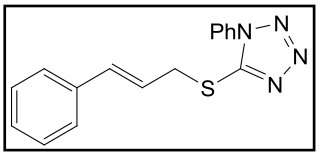
($CDCl_3$, 150 MHz) δ 21.8 ($CH(\mathbf{C}H_3)_2$), 28.4 ($\mathbf{C}HMe_2$), 41.9 ($\mathbf{C}H_2$), 124.0, 129.9 and 130.2 (aromatic **C**H), 133.9 (aromatic **C**), 154.8 (S**C**N); *m*/*z* (CI) 235 (MH^+, 100%); HRMS found 235.1022, $C_{11}H_{15}N_4S$ (MH^+) requires 235.1017.

5-{[(4-Methylphenyl)methyl]sulfanyl}-1-phenyl-1H-1,2,3,4-tetrazole



The crude material was obtained using *Method B.* Purification by flash chromatography (SiO_2, petrol → petrol/EtOAc 19:1) gave the sulfide as a thick pale yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3043, 2922, 1597, 1515, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.33 (3H, s, C**H**$_3$), 4.60 (2H, s, C**H**$_2$), 7.13 (2H, d, *J* 7.9 Hz, $CH_3CC\mathbf{H}$), 7.31 (2H, d, *J* 7.9 Hz, $SCH_2CC\mathbf{H}$), 7.50-7.54 (5H, m, aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.3 (**C**H_3), 37.6 (**C**H_2), 123.9, 129.3, 129.6, 129.9 and 130.2 (aromatic **C**H), 132.2 ($SCH_2\mathbf{C}$), 133.7 (N**C**CH), 138.2 ($CH_3\mathbf{C}$), 154.1 (S**C**N); *m*/*z* (EI) 282 (M^+, 30%), 221 (22), 137 (21), 118 (19), 105 (100); HRMS found 282.0927, $C_{15}H_{14}N_4S$ (M^+) requires 282.0934.

(*E*)-5-(Cinnamylthio)-1-phenyl-1H-tetrazole



The crude material was obtained using *Method B.* Purification by flash chromatography (SiO_2, petrol → petrol/EtOAc 19:1) gave the sulfide as a thick pale yellow oil: υ_{max}/cm^{-1} ($CDCl_3$ cast) 3060, 3027, 1597, 1499; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.21 (2H, dd, *J* 7.5, 1.1 Hz, SC**H**$_2$), 6.36 (1H, dt, *J* 15.7, 7.5 Hz, $SCH_2C\mathbf{H}$), 6.71 (1H, d, *J* 15.7 Hz, PhC**H**), 7.22-7.26 (1H, m), 7.28-7.32 (2H, m), 7.34-7.37 (2H, m) and 7.51-7.60 (5H, m, aromatic C**H**); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 36.0 (**C**H_2), 122.5 ($SCH_2\mathbf{C}H$), 124.0, 126.7, 128.3, 128.8, 129.9 and 130.3 (aromatic **C**H), 133.7 (N**C**CH), 135.3 (Ph**C**H), 136.1 (**C**CH=CH), 153.9 (S**C**N); *m*/*z* (EI) 294 (M^+, 17%), 266 (16), 265 (16), 233 (15), 147 (17), 118 (22), 117 (100); HRMS found 294.0925, $C_{16}H_{14}N_4S$ (M^+) requires 294.0934.

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